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MEDICAL RESEARCH COMMITTEE.

REPORTS

OF THE

CHEMICAL WARFARE MEDICAL COMMITTEE.

No. 14.—THE DELAYED EFFECTS OF
PHOSGENE IN RABBITS, WITH
SPECIAL REFERENCE TO THE IN-
FLUENCE OF MUSCULAR CON-
TRACTION.



October, 1918.

In January, 1918, the Director-General, Army Medical Service, with the concurrence of the Controller of the Chemical Warfare Department, Ministry of Munitions, appointed a special Committee to prepare reports, based upon information received from all sources at the Chemical Warfare Department, for submission to him with a view to their distribution to those concerned, to make suggestions for further co-ordinated medical investigations that may seem desirable, and to advise him generally in respect of the scientific medical aspects of Chemical Warfare. Present constitution of Committee :—

Leonard Hill, M.B., F.R.S. (*Chairman*).
J. Barcroft, C.B.E., F.R.S.
Professor W. M. Bayliss, D.Sc., F.R.S.
Professor A. E. Boycott, M.D., F.R.S., Major, R.A.M.C.
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Lieut.-Colonel H. S. Raper, R.E.
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Colonel A. B. Soltan, C.M.G., M.D.

(With the co-operation of Lieut.*Colonel C. Gordon Douglas, M.C., M.D., R.A.M.C., and Colonel T. R. Elliott, D.S.O., M.D., F.R.S., in France, and of other corresponding members at Porton and in London, Edinburgh, France and Italy.)

REPORTS ALREADY ISSUED.

No. 1. Notes on the Pathology and Treatment of the Effects of Pulmonary Irritant Gases. (*March*, 1918.)

No. 2. The Histological Effects produced by Gas Poisoning and their Significance. (*April*, 1918.)

No. 3. The Symptoms and Treatment of the late Effects of Gas Poisoning. (*April*, 1918.)

No. 4. Polycythæmia after Gas Poisoning and the Effect of Oxygen Administration in the Treatment of Chronic Cases. (*April*, 1918.)

No. 5. The Reflex Restriction of Respiration after Gas Poisoning. (*April*, 1918.)

No. 6. Investigations into the Reaction of the Blood after Gas Poisoning, and the Results of the Administration of Saline and other Substances. The Effects of Bleeding and of the Injection of Calcium Chloride. (*April*, 1918.)

No. 7. Changes observed in the heart and circulation and the general After-Effects of Irritant Gas Poisoning. (*April*, 1918.)

No. 8. Reports on Fatal Cases of Poisoning. (i) Ethyl iodoacetate.

No. 9. Tissue Changes in Animals produced by Pulmonary Irritant Gases. (*September*, 1918.)

No. 10. The Administration of Oxygen in Irritant Gas Poisoning. (*October*, 1918.)

No. 11. Investigations of Chronic Cases of Gas Poisoning. (*October*, 1918.)

No. 12. Treatment of Patients suffering from "Effort Syndrome" by continuous inhalation of Oxygen. (*October*, 1918.)

No. 13. Bleeding after Poisoning by Pulmonary Irritant Gases, with Appendices. (*November*, 1918.)

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THE DELAYED EFFECTS OF PHOSGENE IN RABBITS,
WITH SPECIAL REFERENCE TO THE INFLUENCE OF
MUSCULAR CONTRACTION.

By J. BARCROFT.

March 16th, 1916.

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I.—REPORT FURNISHED TO THE PHYSIOLOGY (WAR) COMMITTEE
OF THE ROYAL SOCIETY, BASED UPON THE INVESTIGATION.

1. Rabbits the day after exposure to phosgene (about 1/60,000 for half an hour) frequently suffer from a species of "shock." The seat of this shock is the central nervous system.

2. The special feature is the depression of the bulbar centres which are associated with the autonomic system.

(a) The general blood pressure is low, the vessels having to some extent lost their tone.

(b) The control of the blood pressure is deficient, so that the pressure in the brain may sink to a dangerous extent when the animal is made to assume the erect position suddenly.

(c) The quickening of the heart which is the normal response to exercise does not take place, but is replaced by a temporary slowing or even momentary stoppage.

3. The respiratory centre becomes involved. Respiration becomes irregular and ceases with fatal results.

4. The amount of muscular contraction necessary to produce death in a rabbit suffering from shock varies with the degree of shock. In the gravest cases of shock the animal dies a quiet death even without exertion, whilst in the mildest, muscular contraction fails to produce fatal results.

5. The cause of the shock is possibly, but not at all certainly, an "intoxication." It is *not* a direct action of absorbed phosgene on the central nervous system. For—

(a) The evidence goes to show that phosgene is not absorbed as such [Hill,* Douglass†].

(b) There are no signs of shock *immediately* after gassing the animal.

6. The exact connection between the muscular exercise and the culmination of the shock in death is as yet doubtful; it may be due to increased hydrogen ion concentration in the blood or tissues, secondary to deficient gaseous exchange. This is much more marked in gassed than in ungassed rabbits for a given degree of muscular exertion.

* Hill, L.

† Douglas, C. G.

} Reports to R.S. War Committee.

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7. The blood of gassed rabbits is usually but not always oxygenated to the normal extent during rest, but not during exercise.

8. No form of artificial respiration, either manipulation of the chest wall or blowing of air or oxygen into the trachea, has restored respiration once the normal respiratory movements have ceased.

Respiration has been restored on the one occasion on which this method was tried, by turning the animal with its feet up and its head down and thus taking advantage of the condition of shock to increase the blood pressure in the brain.

II. WORKERS ASSOCIATED.

The following have given material assistance in this Investigation:—

Dr. Thomas Lewis ...	University College Hospital	Electro-cardiograph.
Prof. Boycott, F.R.S.	University College Hospital	Certain post-mortems.
Captain Guy ...	Northamptonshire Regiment	Blood gas determination and recording.
Mr. Harrison ...	Gonville and Caius College, Cambridge.	Blood gas analysis.
Mr. Castell ...	Christ's College, Cambridge ...	Blood gas analysis.
Miss Cobbold ...	Girton College, Cambridge ... (1, Clare Road, Barton Road.)	Calibrating apparatus.
Miss Dufton ...	} Girton College, Cambridge ...	Experimental assistance.
Miss Jewson...		
Mr. Hogben ...		
	Trinity College, Cambridge ...	Care of animals, &c.

Many thanks are due to Prof. Langley and Prof. Sherrington for kind advice. Prof. Langley has placed all the facilities of the Cambridge Physiological Laboratory at my disposal.

III. CERTAIN MANIPULATIVE DETAILS.

1. *Animals*.—The animals used have been rabbits in every case.

2. *Dose*.—The usual dose has been 1 part of phosgene gas to 60,000 of air for 30 minutes. An appendix is given in which the doses and the fatality are set forth. The doses are tabulated.

3. *Method of Administration*.—The animals were placed in a room the capacity of which was 36,000 litres approximately. This room was fitted with an electric fan, and an air lock at the entrance. The animals we put in the room before the gas was let off. The phosgene was introduced in the liquid form, the standard dose being 2 cc. of the liquid. This was brought in in a sealed glass tube. When the doors were shut the tube, which was warmed by the hand, was broken and the phosgene in most cases evaporated immediately.

All parts of the room were tested with a flame to see that the fan produced a good draught everywhere. The rabbits were always on the ground; the gas was let off about four feet above it.

4. *Method of Imposing Muscular Exercise*.—In some cases we took advantage of struggling movements of the animals due to some accidental circumstance, but in most we induced movements by electrical stimulation.

This was done in the following way except in the cases where electro-cardiograms were taken. An incision was made in the skin

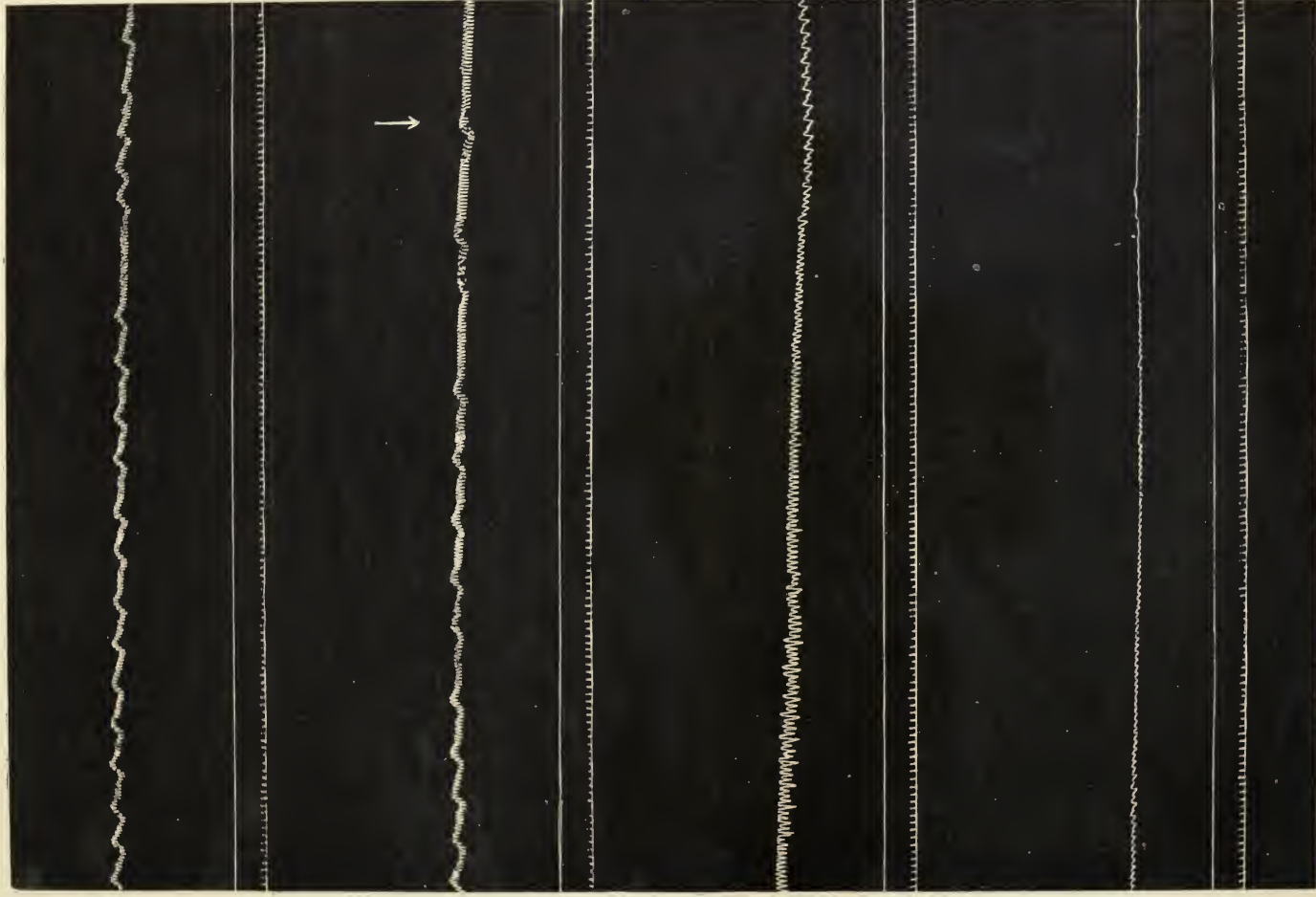


FIG. 1.

[Facing p. 5.]

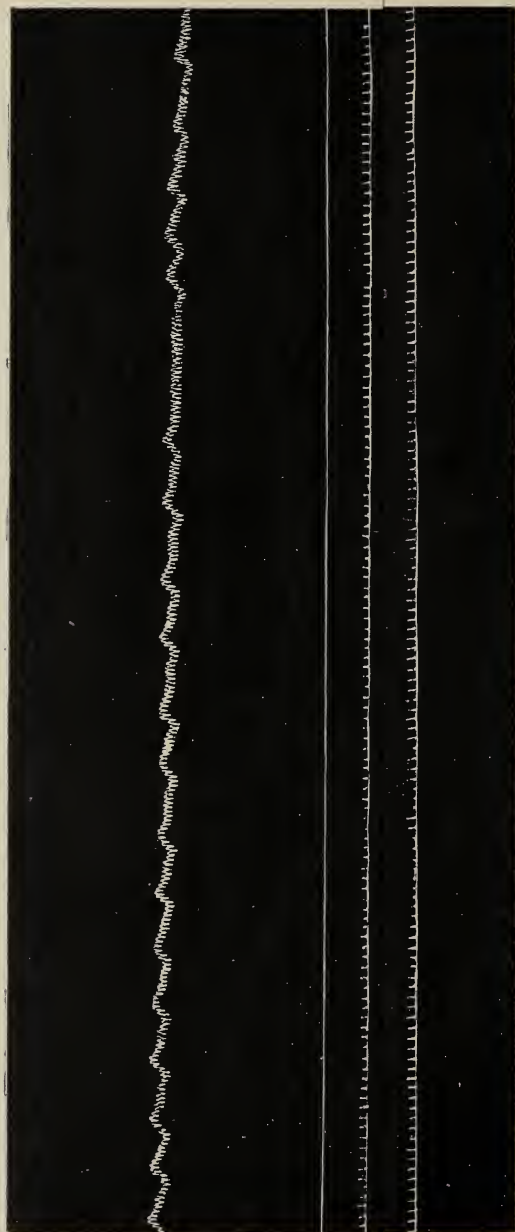


FIG. 1.

[Facing p. 5.]

over the backbone about the bottom of the thoracic region ; another was made above the tail (rabbits anæsthetised). A Spencer-Wells forceps was passed through each incision and fastened to the flesh. These formed the electrodes, and were attached by wires to the induction coil.

Usually a strong faradaic current (coil about 6) was passed through the system for a minute, being interrupted at 2- or 3-second intervals so as to produce spasmodic contractions of a reflex character.

IV. INTRODUCTION.

Quite early in this series of experiments a rabbit died on the operating table as the result of a series of muscular movements, and those of a trivial character. The rabbit (R 5) was gassed the day before with phosgene (1 part of gas to 60,000 of air for 30 minutes). At the time of its death we were making an observation of its mean arterial pressure. A study of the tracing taken will form a suitable introduction to the description of our research (Fig. 1). The tracing has been cut in four, and reads continuously from above downwards. The struggling took place on the top line.

Note :—

- (1) The struggling was not sufficient to affect the general course of the tracing.
- (2) The arterial pressure was low throughout (45 mm. at the commencement of the tracing).
- (3) The respirations became irregular, and stopped, the arrow indicating the last respiration.
- (4) The heart continued to beat after the respirations ceased. It slowed temporarily and gradually became weaker.
- (5) Though the animal died from stoppage of the respiration, there were none of the ordinary vaso-motor reflexes which accompany asphyxia.
- (6) *Post mortem*, the lung on histological examination showed desquamation of the epithelium and some though not much oedema.

These points will be taken up one by one.

V. ARTERIAL PRESSURE.

The same dose of gas which produces death in one animal will produce delayed poisoning in another, and only the most transient effect in a third ; a uniform dose produces a similarly unequal effect on other symptoms. To get any true account of the effect of the gas it is necessary to compare a large number of cases of the gassed rabbits with those of an equal or greater number of cases in ungassed rabbits. The arterial pressure is no exception to this rule.

On the whole the arterial pressure of the gassed rabbits is low.

The observations here referred to are taken by a mercurial manometer connected with a cannula in the carotid artery. The pressure is

measured as soon as possible after the animal has been placed on the operating table.

The following are the arterial pressures so measured :—

Arterial Pressure in Rabbits.

Ungassed.		Gassed.	
No. of Rabbit.	Pressure in mm. of Hg.	No. of Rabbit.	Pressure in mm. of Hg.
55	[142]	29	[112]
41	120	31	98
58	120	48	96
62	118	21	90
9	116	16	76
17	110	30	76
7	109	6	75
33	108	49	74
32	106	5	[64]
47	104		
8	104		
19	100		
13	[88]		
25	[85]		
44	[78]		
	Mean, 110.5 mm.		Mean, 83.6 mm.

N.B.—The cases in brackets were apparently exceptional, and are not included in the computation of averages.

Thus it appears that the arterial pressures of 11 normal rabbits varied from 120–100 mm. with a mean of 110.5, whilst that of 7 gassed rabbits varied from 98–74 with a mean of 83.6 mm. Hg.

It remains to be considered whether the low blood pressure of the gassed rabbits can have had to do with the anæsthetic used. The pressures may therefore be divided into two categories, those of rabbits anæsthetised with luminal and those of rabbits anæsthetised with ether.

Rabbits Anæsthetised with Luminal.

Ungassed.		Gassed.	
Rabbit.	Blood Pressure.	Rabbit.	Blood Pressure.
9	116	21	90
17	110	16	76
7	109	6	75
8	104	5	64
19	100		
13	88		
25	85		
	Mean, 102		Mean, 76

Rabbits Anaesthetised with Ether.

Ungassed.		Gassed.	
Rabbit.	Blood Pressure.	Rabbit.	Blood Pressure.
53	142	29	112
41	120	31	98
58	120	48	96
62	118	30	76
33	108	49	74
32	106		
47	104		
44	78		
	Mean, 112		Mean, 91

From the above tables it is evident—

- (1) That the blood pressures with ether are on the whole higher than with luminal. This is true both of the gassed and the ungassed rabbits.
- (2) That whether ether or luminal be used the ungassed rabbits have a higher BP than the gassed ones.
- (3) The ungassed luminal rabbits have a higher pressure than the gassed ether rabbits.

Whilst it would be desirable to have many more experiments it seems clear that the low blood pressures observed in the gassed rabbits cannot be accidental.

At this stage it may be desirable to tabulate the arterial pressures relatively to the degree of poisoning of the animal in so far as it may be judged from the type of death.

Gassed Rabbits.

Rabbit.	Arterial Blood Pressure.		Death.
29	...	112	Natural respiratory movements ceased on operating table after tetanisation, artificial respiration, thorax open.
31	...	98	Survived intermittent tetanus, killed by asphyxia.
48	...	96	Respiration stopped and animal apparently died after tetanising with "feet down." Resuscitated.
21	...	90	Survived 1 minute intermittent tetanus in horizontal position. Killed.
16	...	76	Died owing to tetanus.
6	...	75	Not tetanised. Killed.
49	...	74	Accidental.
5	...	64	Died on operating table, slight struggling.

In seeking a cause for the low arterial pressure one may say that evidence of gross cardiac inefficiency was absent.

In Figs. 2, 3 and 4 the blood pressure tracings are given of—

- (Fig. 2) The ungassed eight rabbits with the highest blood pressure.
- (Fig. 3) The ungassed eight rabbits with the lowest blood pressure.
- (Fig. 4) Eight gassed rabbits.

The actual heart beats on many of the curves are indistinct (the undulations plainly visible on most being respiratory), but inspection of the heart and the general characters of the pulse showed no striking differences in general nature (as regards rapidity, &c.) between the gassed and the ungassed rabbits. The same is true of the string galvanometer tracings.

The cause of the low blood pressure is then to be sought in the following sources either singly or combined—

- (1) The nervous system—
 - (a) Central ;
 - (b) Peripheral.
- (2) The muscular wall of the blood vessels.
- (3) Deficiency in the volume of circulating fluid.

1. *Nervous System*.—Stimulation of the distal ends of such nerves as the cervical sympathetic produced their usual effects with minimal faradaic currents. So far, therefore, as the nervous system is concerned, deficiency of vaso-motor tone in this as in other typical cases is due either to central inhibitory influences or to deprivation of normal central augmentor impulses upon the muscles of the arteries. In other words, it is apparently central in origin, not peripheral.

2. *The Muscular Walls of the Blood Vessels*, as indicated above, appear to be capable of their usual response.

3. *Deficiency of Volume in the Circulating Fluid* has as yet not been investigated, but will form the result of a separate communication.*

[Note added September, 1917.—Whilst this research was in progress Dale, unknown to us, was working at the relation between shock from abdominal lesions and a diminution in the volume of the circulating fluid, but with no special reference to gas poisoning. That such a deficiency exists in the first 24 hours of gas poisoning appears from the results obtained by one of us (Miss Dufton) after we knew of Dale's work on abdominal lesions. It seemed to us probable that lesions of the lung produce shock which is essentially of the same type as lesion of the abdomen. We have to thank the Secretary of the Medical Research Committee for keeping us in touch with Dale's work.]

Before leaving the question of arterial pressure allusion should be made to rabbit 38, which, unlike other gassed rabbits, was operated upon immediately after it was gassed. This rabbit had a good blood pressure (*see* Fig. 5). This with other symptoms to be related suggests that the poisoning is not due to a primary effect of the gas.

* This investigation forms the subject of the report entitled "Acute Oligæmia and Secondary Polycythæmia after Gas Poisoning," by Dorothy Dufton.—*Reports of the Chemical Warfare Medical Committee*, No. 4, April, 1918.

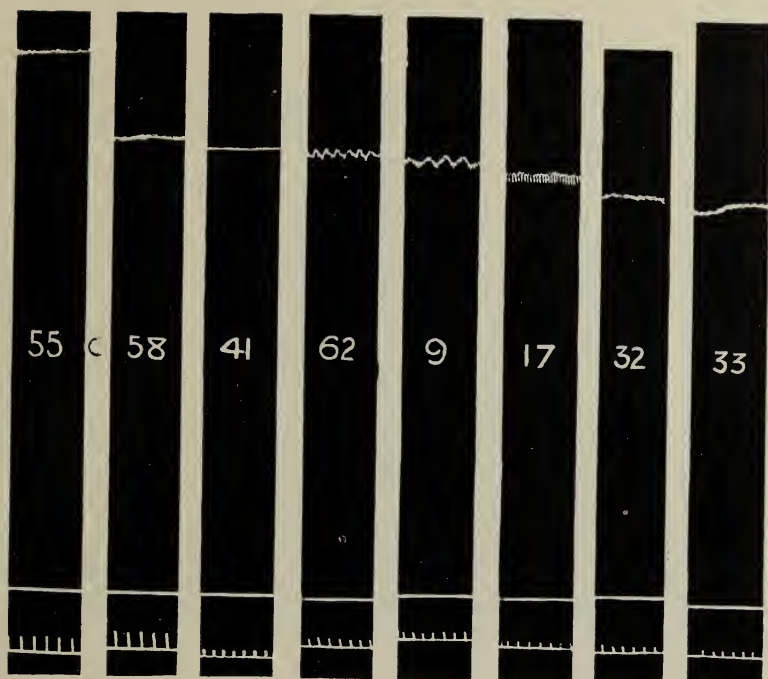


FIG. 2.

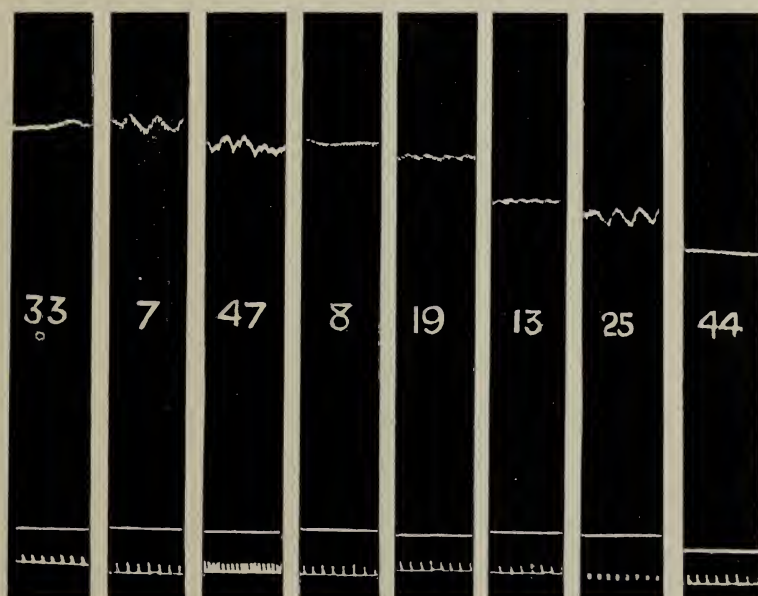


FIG. 3.

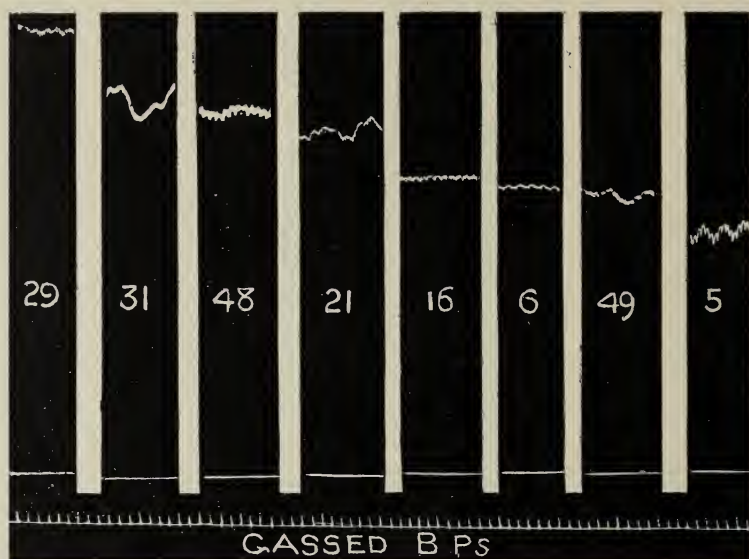


FIG. 4.



FIG. 5.

VI. RESPIRATION.

So far as we have been able to judge the moment of death must be reckoned as that at which the respiration ceases.

We have made observations both on anæsthetised animals and unanæsthetised animals always with the same result ; muscular movements, if they produce death, do so by stopping the respiration. The heart may go on for an indefinite period, indeed so independent is the heart beat of the respiration that in all cases in which the animal has been killed by muscular movement we have opened the thorax and found the heart beating.

We have already seen that the vaso-motor centre seemed to be depressed. The unsteadiness of the respiration prior to its cessation and the cessation of respiration itself seem also to point to depression and ultimate abolition of function of the respiratory centre.

All efforts which we have so far made to revive the animal by means of artificial respiration once it has ceased breathing naturally have failed. In this connection it must be borne in mind that the ordinary methods of applying artificial respiration by manual manipulation involve putting pressure on the thorax. As there is usually some œdema in animals which die of delayed phosgene poisoning, the effect of squeezing the thorax is to press the fluid out of some of the alveoli of the lung into the bronchi, and thus to make the pulmonary conditions worse.

Whether by manipulation or by attaching one limb of a Y-shaped trachea tube to an oxygen cylinder and alternately opening and closing the other so that the thorax became alternately inflated and deflated, *we have found artificial respiration useless as a restorative.*

Whilst we have found artificial respiration useless as a restorative, we have had no difficulty in keeping the animals alive with artificial respiration from a pump. One experiment of this sort (R 29) was instructive ; the thorax was open and artificial respiration maintained since its object was the inspection of the heart—but that is foreign to the present argument. Here we would draw attention to the fact that concurrently with artificial respiration, the natural respiratory movements were continued until the animal's muscles were thrown into rhythmic contractions by the administration of a faradaic current to electrodes on the skin. After the muscular spasms the natural respiratory movements ceased, and though the artificial respiration was continued, the natural respiratory movements did not return.

Short of actually stopping the respiration, stimulation of the skeletal muscles may slow it. Thus in rabbit 16, 15 seconds' stimulation of the rabbit's back slowed the respirations very obviously. These phenomena are only to be observed as far as we know in gassed rabbits. When the stimulation was stopped the respirations soon recovered, but on giving another 15 seconds' stimulation the respirations stopped and the animal died.

VII. THE HEART.

Experiments of two kinds have been carried out on the heart.

- (1) The electro-cardiogram observations.
- (2) Records of arterial pressure under various operative procedures.

I. *Electro-cardiographic Observations with the String Galvanometer.*

—The general course of these may be described as follows:—They fall into two groups—in both of which animals were made to take muscular exercise by the administration of electric shocks or otherwise. The groups are divided as follows:—

- (a) Cases in which the exercise was fatal.
- (b) Cases in which it was not.

The electrodes in all cases were placed on shaved patches of skin immediately above and below the sternum.

These electrodes each consisted of a halfpenny to which a wire was soldered. They were attached to the skin by plaster and served both as “leads” for the string galvanometer and as electrodes for the administration of the faradaic current.

As an introduction, two tracings (Figs. 6 and 7) may be described. They are from an *ungassed* rabbit before and after faradisation.

The two points to note are—

- (1) The already rapidly beating heart of the normal rabbit (Fig. 6) quickens slightly (Fig. 7). The upright rulings on all the galvanometer tracings correspond to fifths of seconds.
- (2) The exaggerated T, in the exercised rabbit, is due, so it is presumed, to *sympathetic stimulation* of the heart, and accompanies acceleration.

One pictures, then, cardiac acceleration—in part the result of sympathetic stimulation—as taking place normally when the muscles are exercised.

The nature of stimulus which, through the sympathetic system, effects this acceleration is not known. The rapidity of the onset of cardio-acceleration, as shown by Krogh and Lindhart and others, suggests that in its initiation, at all events, it is due to an apparent nervous rather than a chemical stimulus to the medulla oblongata.

It is quite likely that the effect of the afferent stimulus (whatever it may be) on the medulla may not be simple. Many of the medullary centres may be stimulated and the stimulation may not escape the cardio-inhibitory centre. Indeed, what we have to say presently will be most easily explained if we suppose that both cardio-augmentor and cardio-inhibitory centres are stimulated but that the augmentor centre gets the upper hand.

With this picture of the effect of exercise on the electro-cardiogram tracings of the normal rabbit, let us turn to the gassed rabbit.

Fig. 8 shows two electro-cardiograms of the heart beats of a rabbit gassed the day previously. After the record was taken the rabbit

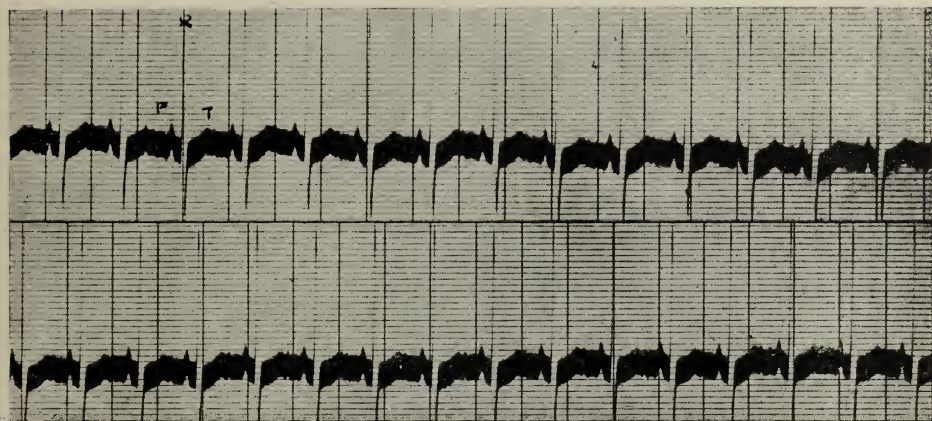


FIG. 6

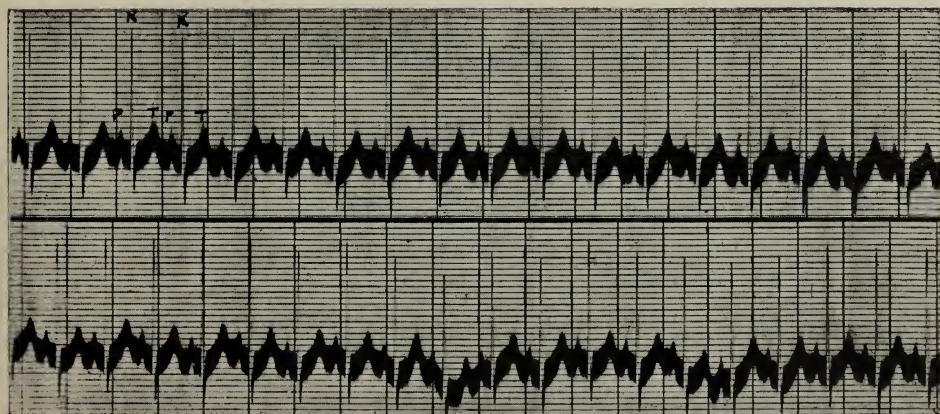


FIG. 7.

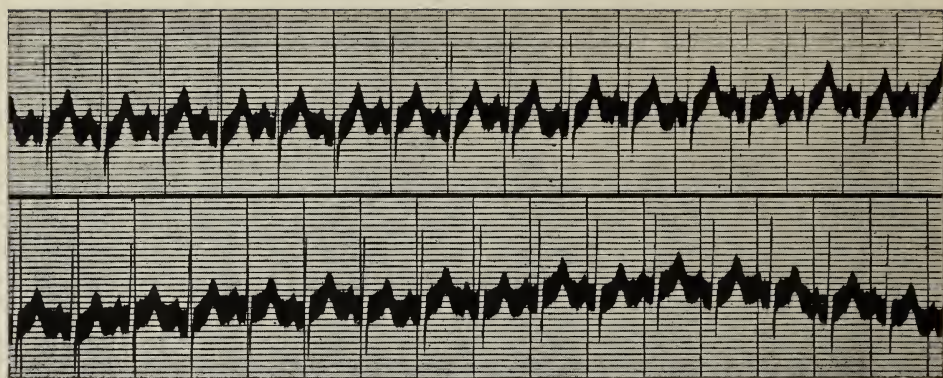


FIG. 8.

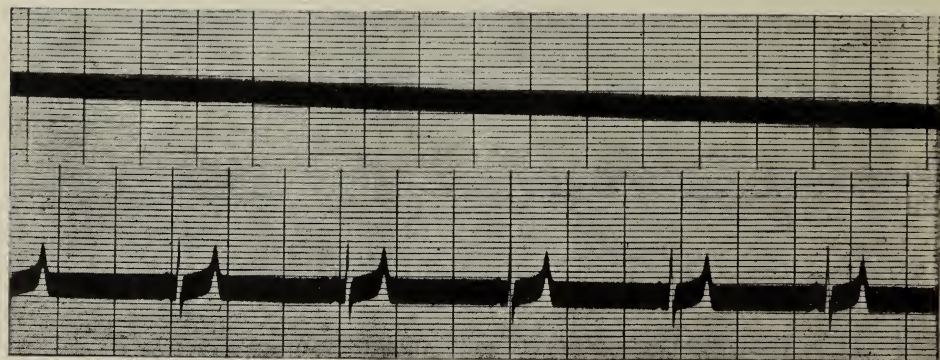


FIG. 9.

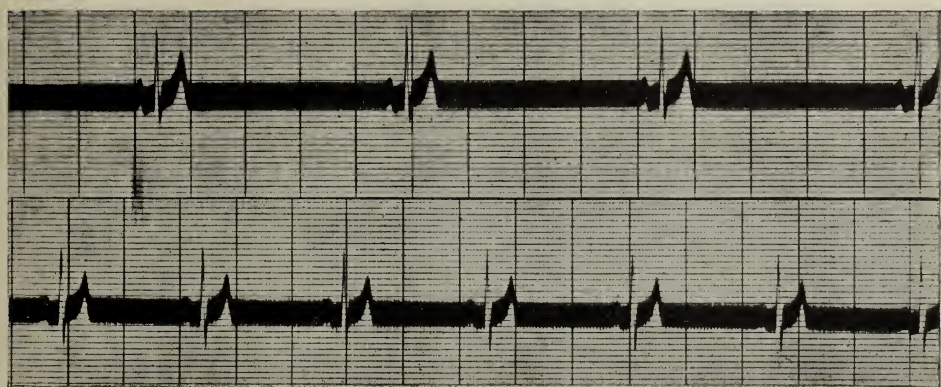


FIG. 10.

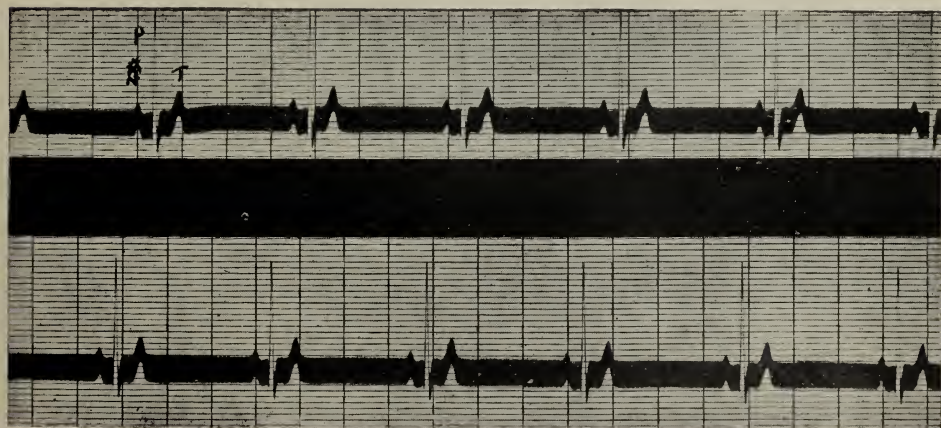


FIG. 11.

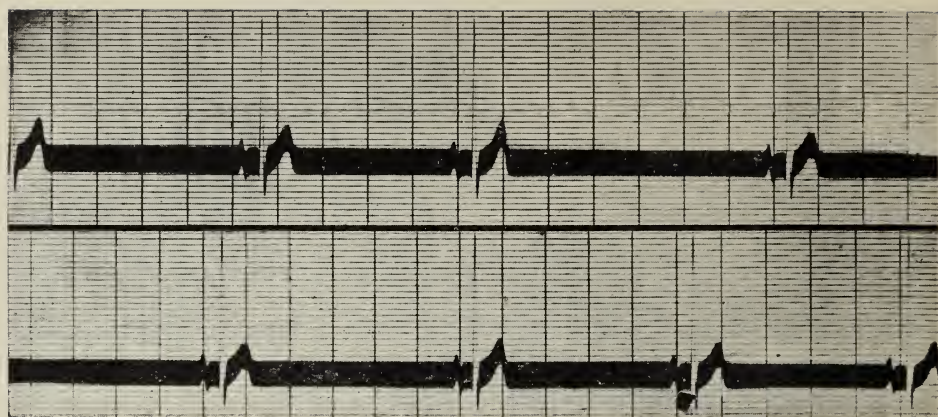


FIG. 12.

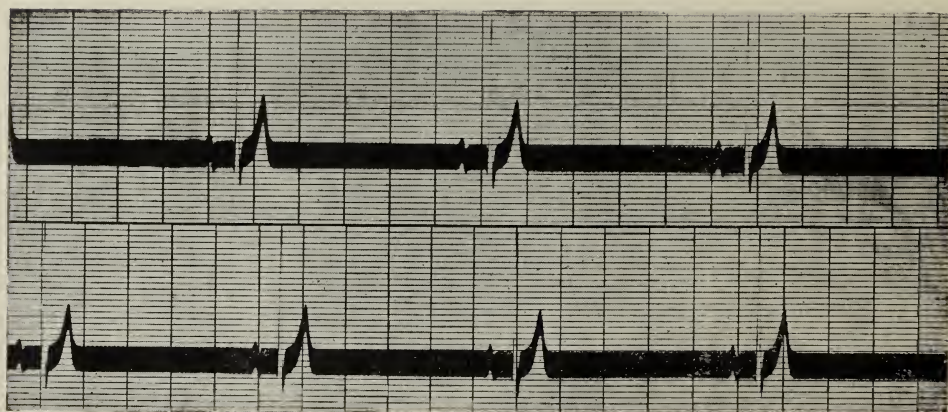


FIG. 13.

was subjected to a faradaic current for 30 seconds, with the result that it gave a number of muscular contractions and then ceased to respire. Respiration was never restored. Immediately a couple of records (Fig. 9) were taken; in the first the whole plate passed the string without a single heart beat (about 3 seconds), in the second the heart beat had quickened to about one beat in $3/5$ seconds. Two minutes later another pair of records was taken, at the end of which the heart quickened considerably (Fig. 10).

These tracings suggest that in fatal cases of delayed poisoning with phosgene temporary stoppage or slowing of the heart takes place as well as stoppage of the respiration, but that whereas the respiratory stoppage is permanent the cardiac stoppage is not necessarily so. This view is in accordance with what took place in rabbit 5, quoted in the introduction, but it needs confirming by control experiments of several kinds.

(a) The first question which might arise is as follows: Is the slowing exhibited in R 10 in any way due to the faradaic current with which the rabbit was stimulated, rather than to the muscular exercise which the rabbit took?

The question is answered in several ways.

- (1) Rabbit 3—gassed—died in way quite similar to rabbit 10 except that the struggling which gave rise to death was not induced by electrical stimulation, but to opposition on its part to the preparation required for applying the electrodes. (Subsequently, it became our practice to shave the necessary portions of rabbits the day previously.) No sooner were the electrodes firmly on than the rabbit after struggling breathed its last. We had no record of the heart beats before death. From numerous tracings of other rabbits we have no doubt it was in general similar to Fig. 8. We have three records taken, 4, 5, and 7 minutes after death (Figs. 11, 12 and 13). They all show the very slow heart beat. But in Fig. 11 there is no drawing out of the P.R. interval typical of an asphyxial slowing. This exaggerated P.R. interval is well seen in Fig. 13. The slowing shown in Figs. 9, 10 and 11 is therefore presumably vagal, not asphyxial—a presumption supported by other evidence.
- (2) There is abundant evidence from blood-pressure tracings, in which we observed slowing of the heart during or immediately after natural struggling in gassed rabbits to show that the phenomenon of cardiac slowing (R. 48), whatever its immediate cause, is remotely the result of muscular movements, and is not the direct result of stimulation of the skin or subcutaneous structure with a faradaic current.

(b) Let us now turn to the immediate cause of the cardiac slowing.

Emphasis has already been laid on the fact that there is no shortening of the P.R. interval and, therefore, so far as the electrocardiogram records help us, we must consider it to be due to the influence of the medullary cardiac centres rather than to the effects of chemical products of activity upon the tissue of the heart.

II. *Evidence from records of Arterial Pressure.*—The view that the cardiac inhibition is nervous is supported by other evidence. In several experiments we have cut the vagi and either abolished it or observed that it failed to make its appearance when muscular exercise took place. A good example of this is seen in Fig. 14A. The struggling was induced by the simple process of altering the posture of the rabbit. Consequent on the struggling is seen the cardiac inhibition. Whilst the vagus inhibition was still marked, as shown, by the slow deep rhythm, the animal started a second series of struggles; the vagi, which had previously been prepared, were cut and the heart at once resumed its normal rapid beat. A similar case is shown in Fig. 14B.

Such a tracing as that shown in Fig. 14A may be deceptive in this way. The undulations which look like vagus beats may really be spasmodic rises of blood pressure due to rhythmic struggling movements. In this experiment we were careful to notice the shimmer of the blood in the arterial cannula throughout and to satisfy ourselves that the undulations in the tracing synchronise with the heart beats.

So far, we have spoken only of fatal cases of phosgene poisoning—in these death was produced by muscular movements either spontaneous or produced by passing shocks into the skin. In some cases the animal has survived such treatment.

For instance, rabbit 4, a week after the records already shown (Figs. 6, 7, 8) were taken, was again the subject of experiment. It was gassed the day before, treated in a manner quite similar to R 10, the heart showed no sign of slowing. The same was true of rabbits 11 and 12.

Yet once more, a week later, was rabbit 4 gassed, its electrocardiogram record on this occasion showed irregularities in the form of extra systoles. This we mention rather for the purpose of noting how free our tracings have been of anything of this kind. From the day of the first gassing we have never noticed fibrillation.

Whilst vagus slowing of the heart may be regarded as a cause contributory to death in cases of delayed phosgene poisoning, it cannot be regarded as the cause of death. For in several experiments in which the vagi have been cut we have yet been able to kill the animal (R 48), *i.e.*, to produce permanent cessation of respiratory movements by inducing muscular movements.

R 29 and 30.—Two experiments were performed on the heart to ascertain by inspection whether there was any evidence of dilatation of the heart or fibrillation.

Neither showed any sign of fibrillation. R 30 showed some distension of the right side of the heart, which increased when the rabbit was tetanised. R 29, however, was quite free from dilatation, even though the rabbit died after the application of the faradaic current.

R 30 was singular among our rabbits in having dark arterial blood; how far this fact was connected with the cardiac dilatation and in what way are matters for future enquiry. The immediate point

STRUGGLING: NO ELECTRICAL STIMULUS

THESE ARE HEART BEATS, NOT STRUGGLES.

VAGI CUT



FIG. 14A.—TIME MARKER INDICATES SECONDS.

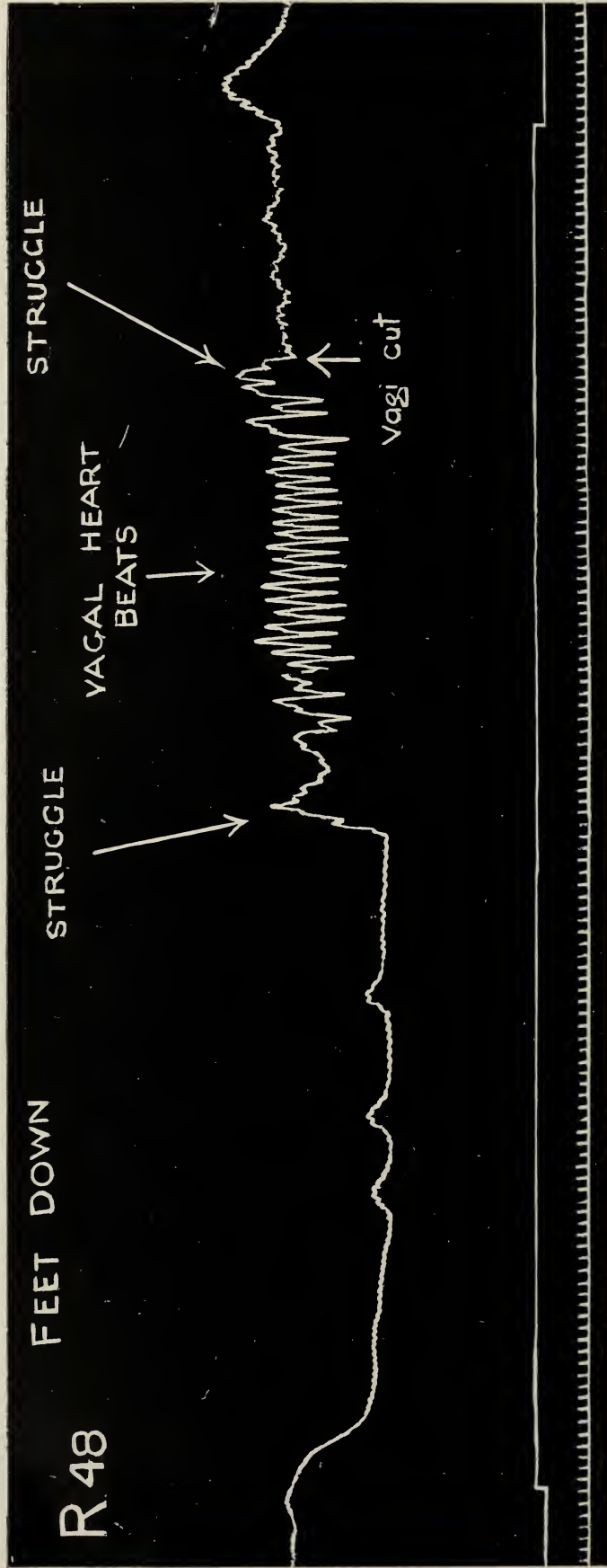


FIG. 14B.

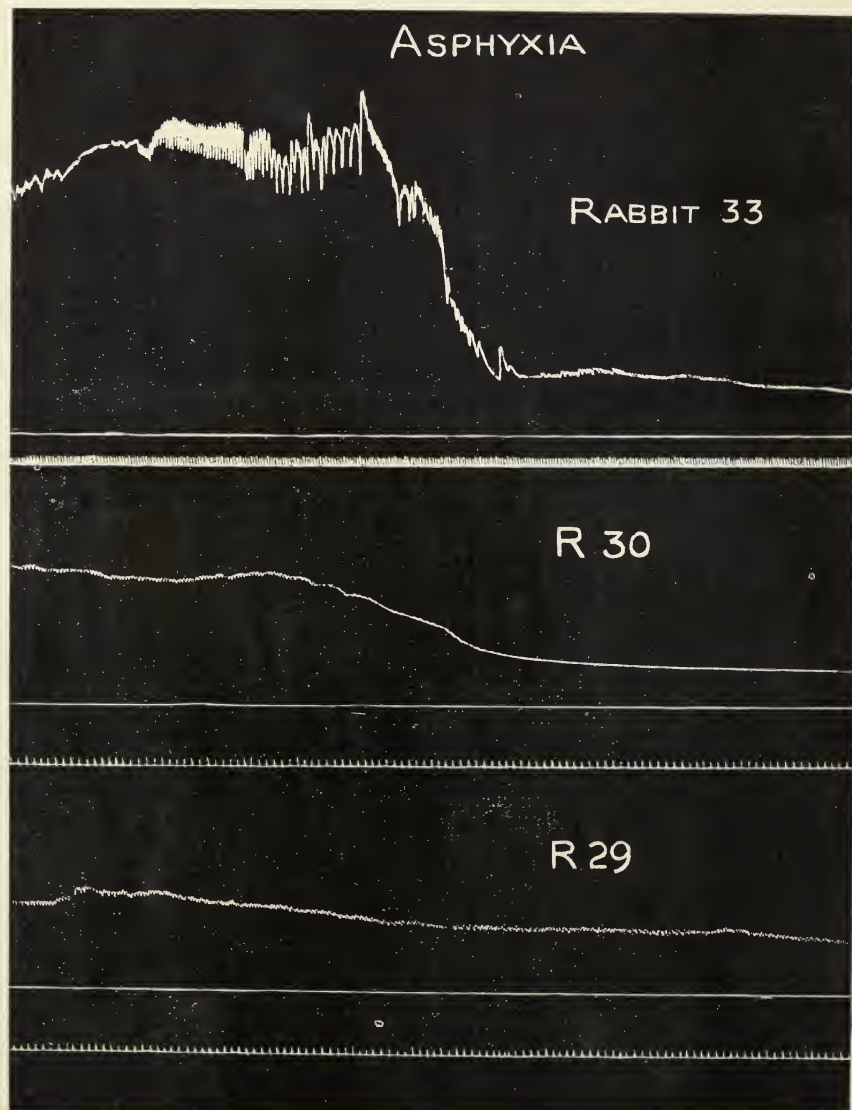


FIG. 15.

[Facing Fig. 14B.

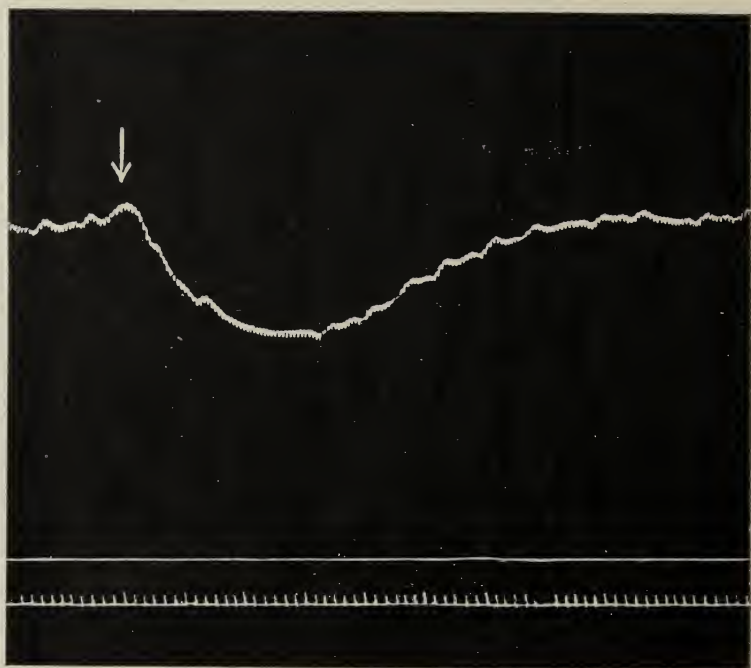


FIG. 16A.

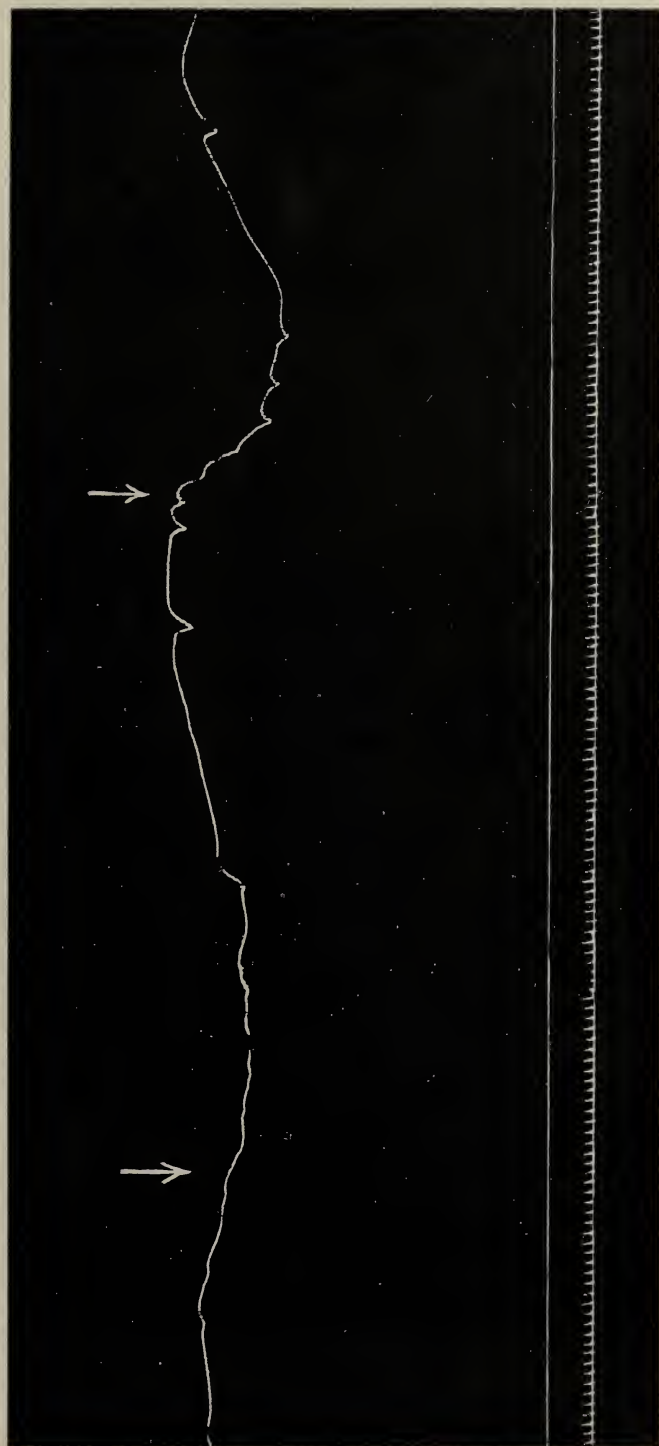


FIG. 16B

[Facing Fig. 16A.]

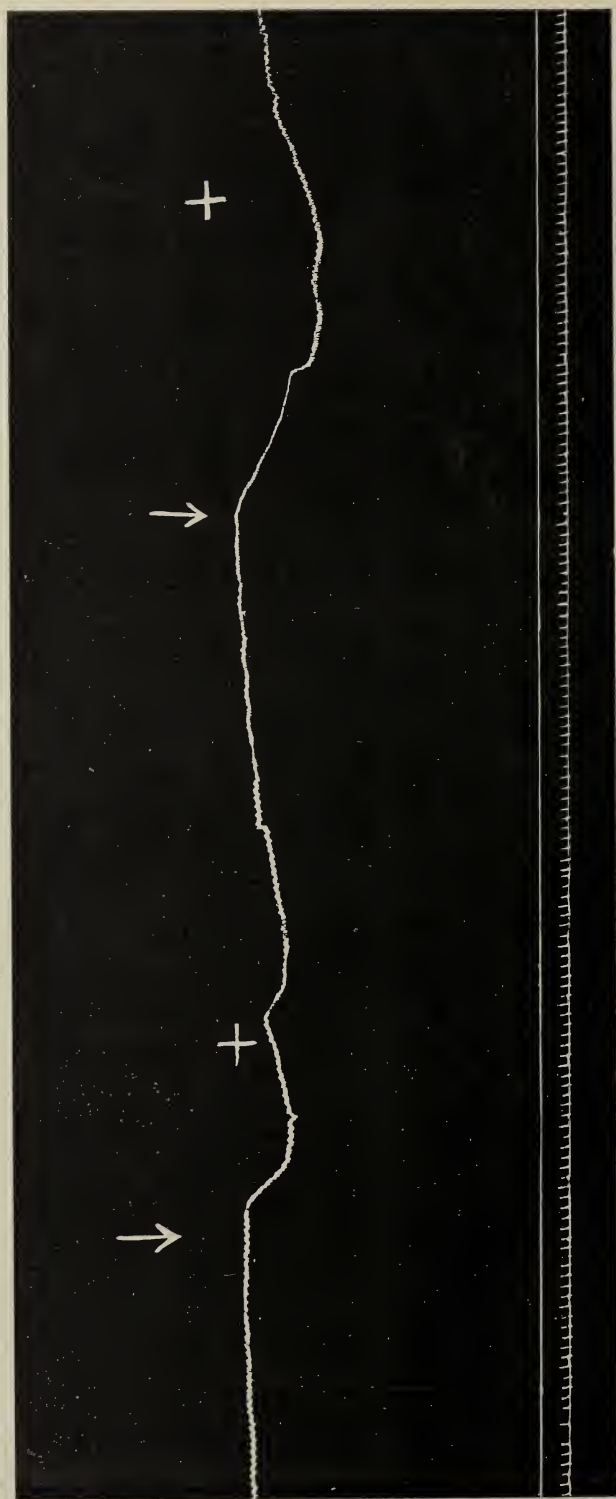


FIG. 16c

[Facing p. 13.]

is clear, namely, that cardiac dilatation is not the cause of the conditions found in delayed gas poisoning.

These facts bear out the view expressed by Hill at the Royal Society Committee (March 9th, 1916), that heart failure was not the cause of death in delayed gas poisoning.

VIII. VASO-MOTOR REFLEXES.

Each factor which we have investigated so far has pointed to the medulla, or at all events the central nervous system as being the seat of those changes which prove fatal.

- (1) The low arterial pressure is due to lack of functional activity of the vaso-motor centres.*
- (2) The cardiac slowing is due to lack of power on the part of the sympathetic centre to assert itself.
- (3) The cessation of respiration is due to the apparent poisoning of the respiratory centre. Moreover in tracings of death from acute asphyxiation we observe in gassed rabbits (29 and 31) that the ordinary vaso-motor changes which accompany acute asphyxia are not evident in the tracing.

Fig. 15 shows three tracings. The top one is that of a normal rabbit dying of asphyxia, the trachea being clamped at the point indicated by the commencement of the tracing.

The two lower tracings are those of gassed rabbits in which asphyxia was induced either by stoppage of artificial respiration or ligature of the trachea. In both cases there is an absence of the rise of blood pressure and struggling movements usually associated with acute asphyxia.

These facts pointed to a lack of vaso-motor response to stimuli. Professor Langley suggested that stimulation of the depressor in gassed rabbits might furnish instructive results.

Several experiments were carried out both in gassed and normal rabbits for the purpose of comparing the responses obtained from stimulation of the depressor.

In normal rabbits we have not invariably got a good depression of the arterial blood pressure, when the central end of the depressor was stimulated. Figs. 16A and 16B show the result of three stimulations of the depressor in normal animals. The depression amounted to 40 per cent., 11 per cent. and 32 per cent. respectively of the arterial pressure.

In gassed rabbits we have never obtained a good depression; frequently we have observed none, but those shown in Fig. 16C are the best which have befallen us, and clearly they fall short of two of those in Figs. 16A and 16B both in respect of the promptitude and of the magnitude of the response as expressed by the proportion of depression to the total pressure. The greatest depression is 25 per cent. of the arterial pressure.

* Prof. W. B. Cannon suggests that the lessening of blood volume is a possible factor (January, 1918).

The deficiency of vaso-motor reflex action is more marked, however, when we are studying a reflex, which should augment the arterial pressure rather than one which should depress.

The lower tracing in Fig. 17 shows the best of a few efforts to raise the arterial blood pressure in a gassed rabbit by stimulation of the central end of the divided sciatic nerve. The space between the two arrows on the tracing signifies the interval of time during which the sciatic was stimulated. The upper tracing in the figure shows the result of a similar stimulation to a normal rabbit. In comparing these tracings, two points should be borne in mind :—

- (1) The rabbits were not curarised, and therefore the muscular movements may have done much to promote a rise of pressure in the ungassed rabbit, in which they were more considerable.
- (2) The drum was moving much more slowly in the top tracing, thus giving an accentuated appearance of suddenness to the rise. In each case the time marker indicates seconds.

These considerations, however, do not alter the extremely poor response given by rabbit 16, and, as we have said, it was the best of the few which we tried.

Finding that the vaso-motor centre did not respond vigorously to artificial afferent stimuli, we naturally asked ourselves whether it would respond to the stimuli which influence in normal life. We there decided to observe the effects of variations in posture. The alteration of posture was carried out as follows: The rabbit was lying horizontally on the back tied to a small dissecting board. The board was taken in the hands and rotated about an axis coinciding in position with the cannula in the carotid artery, till it reached the vertical position, either with its head or its feet uppermost as the case might be.

In the great majority of cases when the normal rabbit was changed from the horizontal to the vertical, feet-down position (which we shall call the "erect" position), the blood pressure, after a temporary drop, recovered itself approximately. In some cases, as in Fig. 18, the vaso-motor centre slightly over-compensated, so that the arterial pressure became slightly higher in the erect than in the recumbent position. More frequent are such cases as are shown in Fig. 19, which we may regard as typical, whilst only occasionally do we obtain failure to compensate; the most marked case of this kind is the last shown in Fig. 20. (The anæsthetic used was ether, and the animal was slightly under its influence.)

In gassed rabbits failure to compensate is not the exception but the rule. The fall of pressure may be more or less, but in either case the depression remains until the animal is replaced in the recumbent position. Figs. 21 and 22 give typical examples of this fact.

In rabbit 48 (Fig. 23) the fall of blood pressure was less than in those figured above, but the failure to restore the pressure to the normal level was even more marked, and it showed a gradual decline (see Fig. 23). This rabbit may have been somewhat exceptional owing to the fact that its vagi were cut.

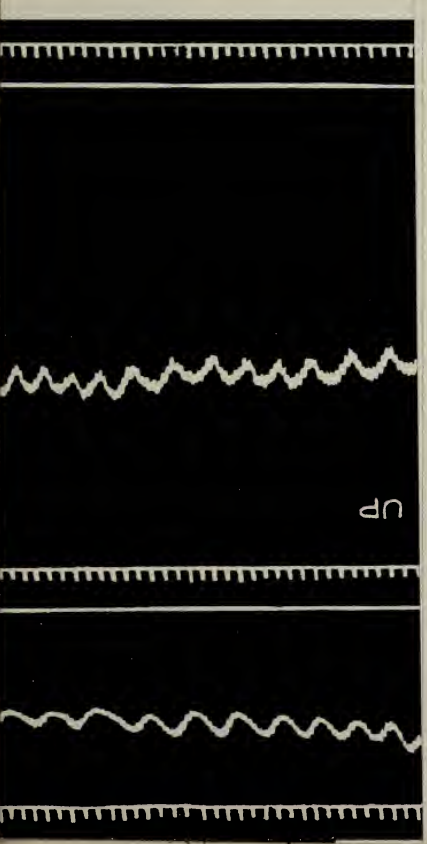
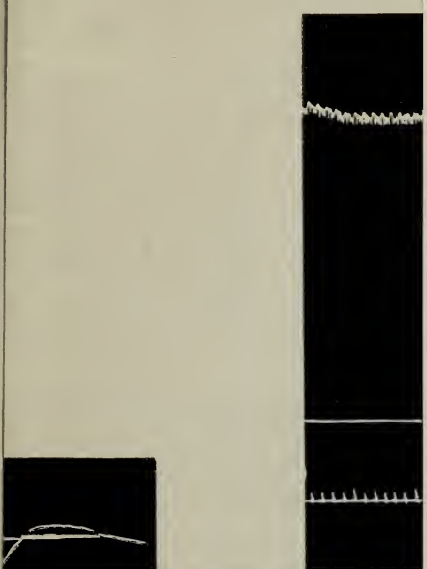
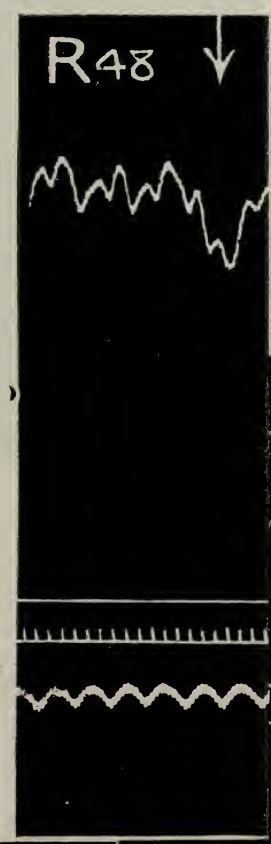
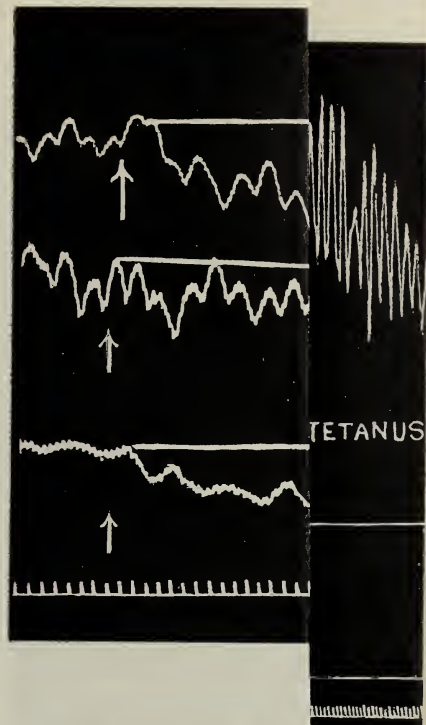


FIG. 48, EARLIER THAN FIG. 23, VAGI INT.

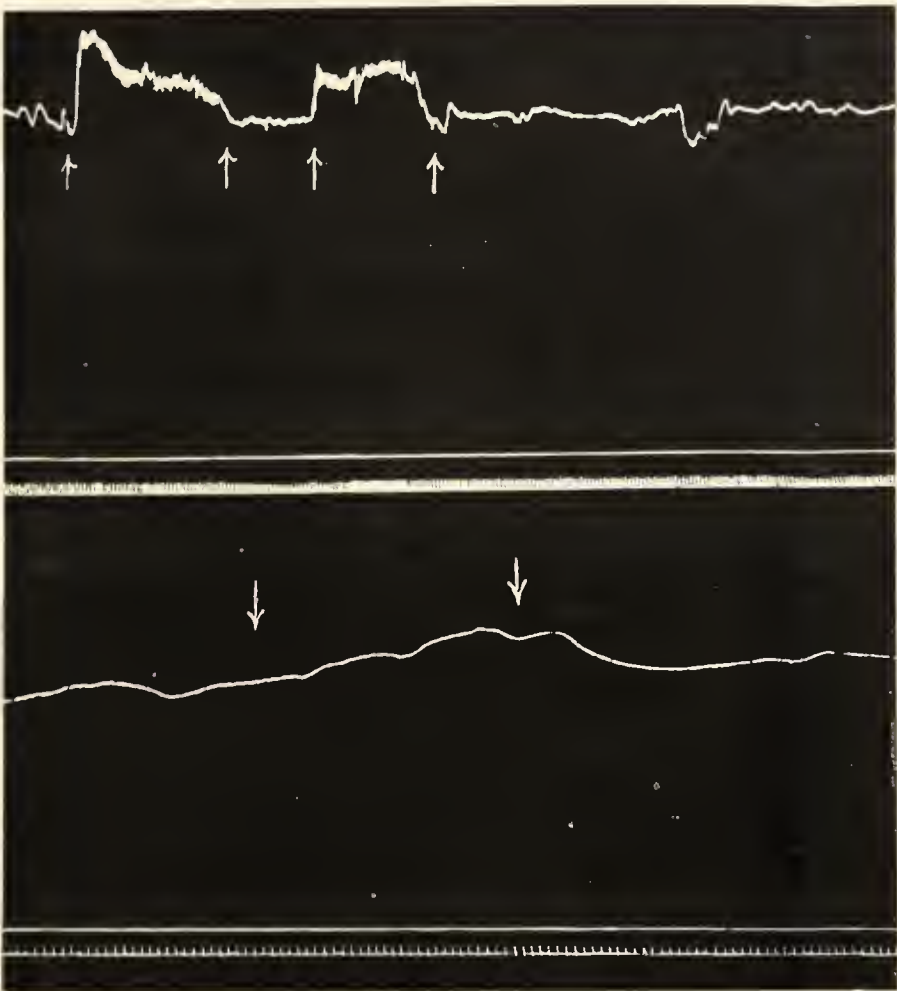


FIG. 17.

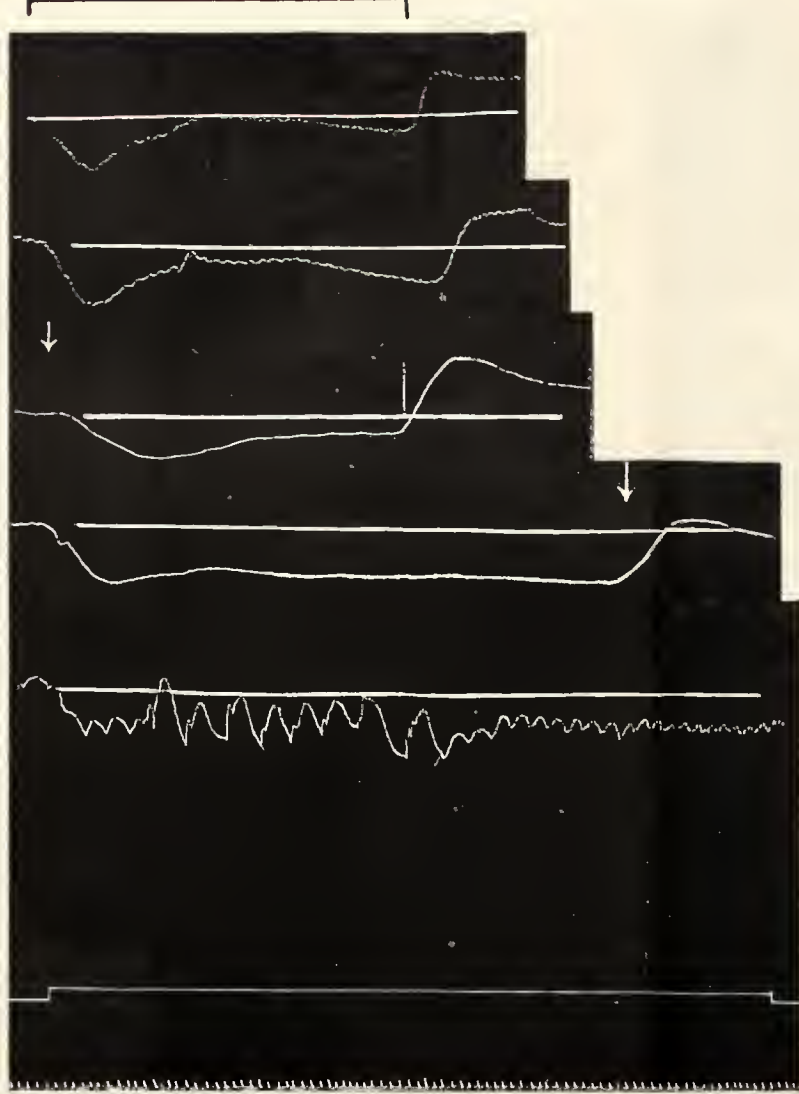


FIG. 19.

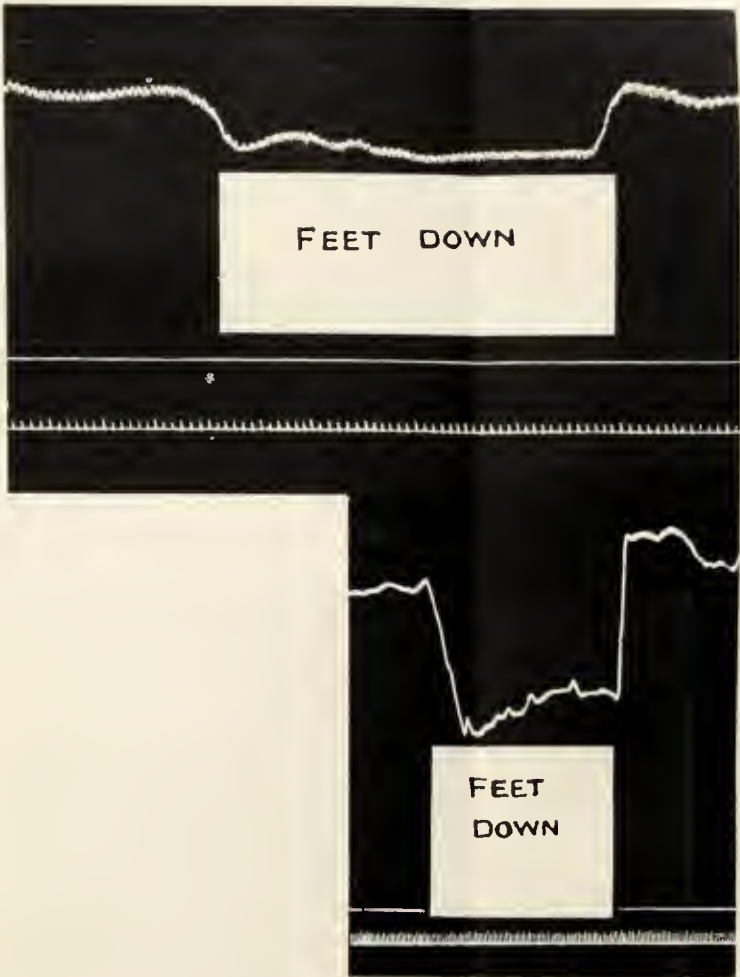


FIG. 22.

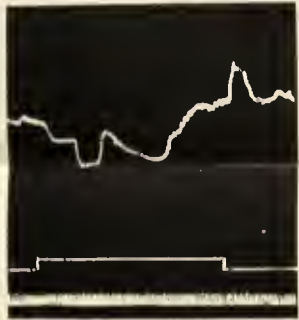


FIG. 18.



FIG. 20.

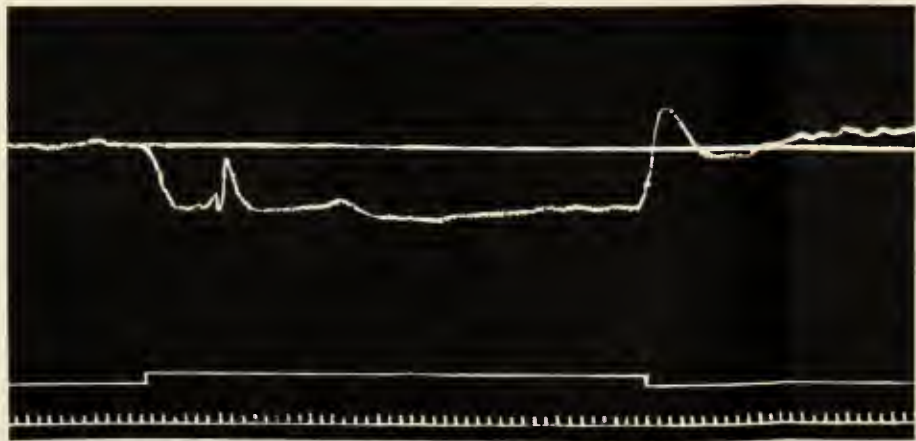


FIG. 21.

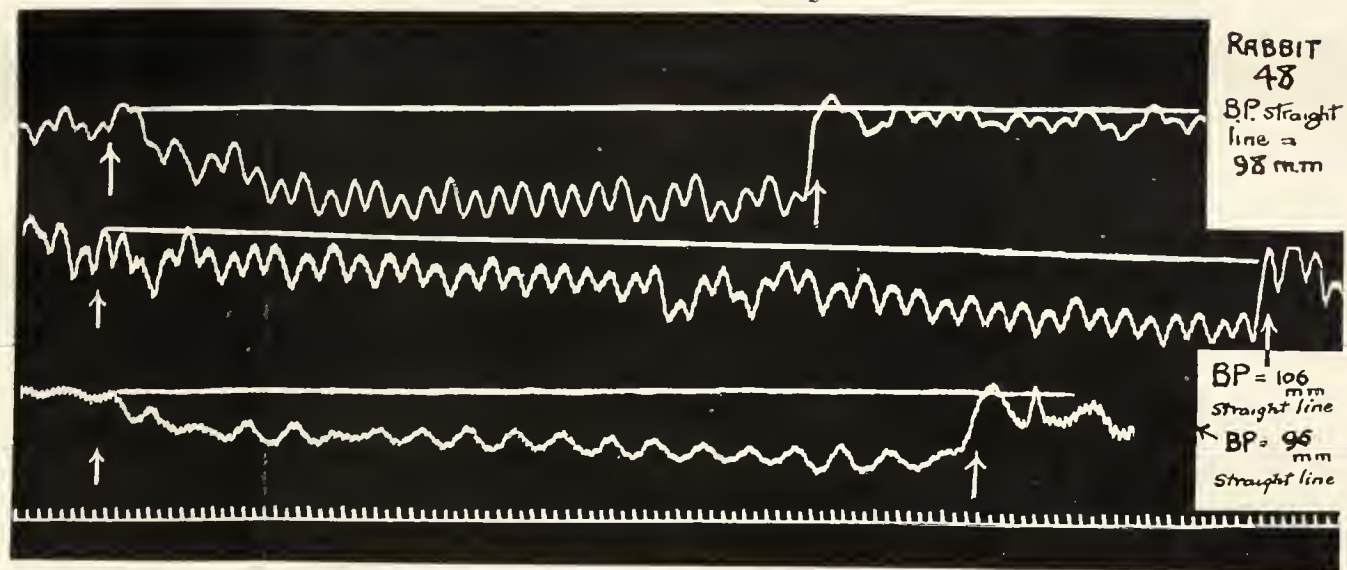


FIG. 23.—BLOOD PRESSURE OF RABBIT 48 AFTER SECTION OF VAGI.

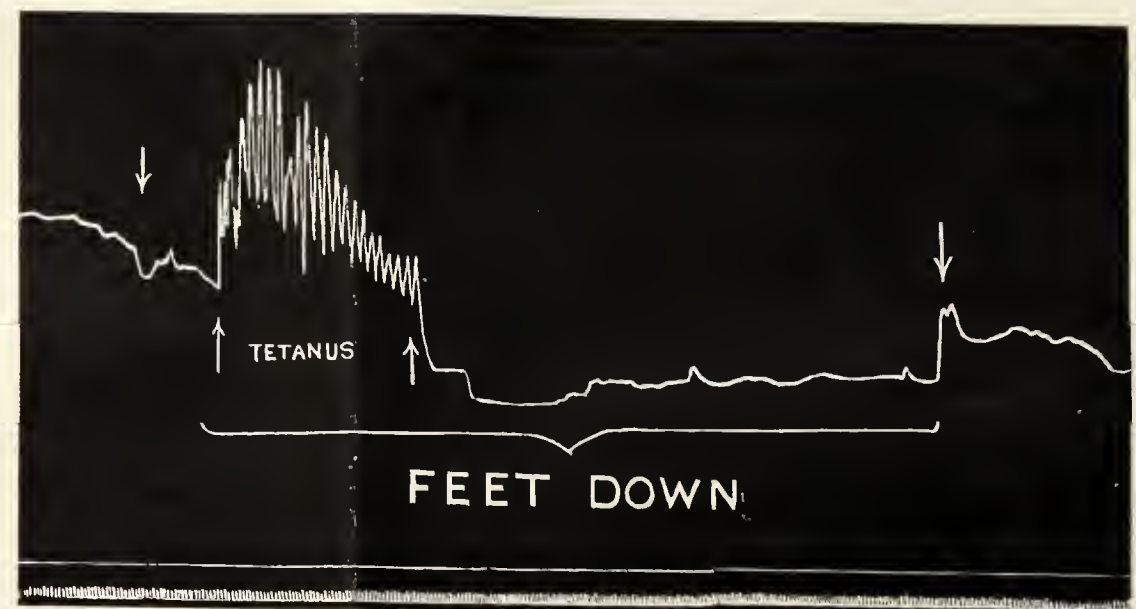


FIG. 25.

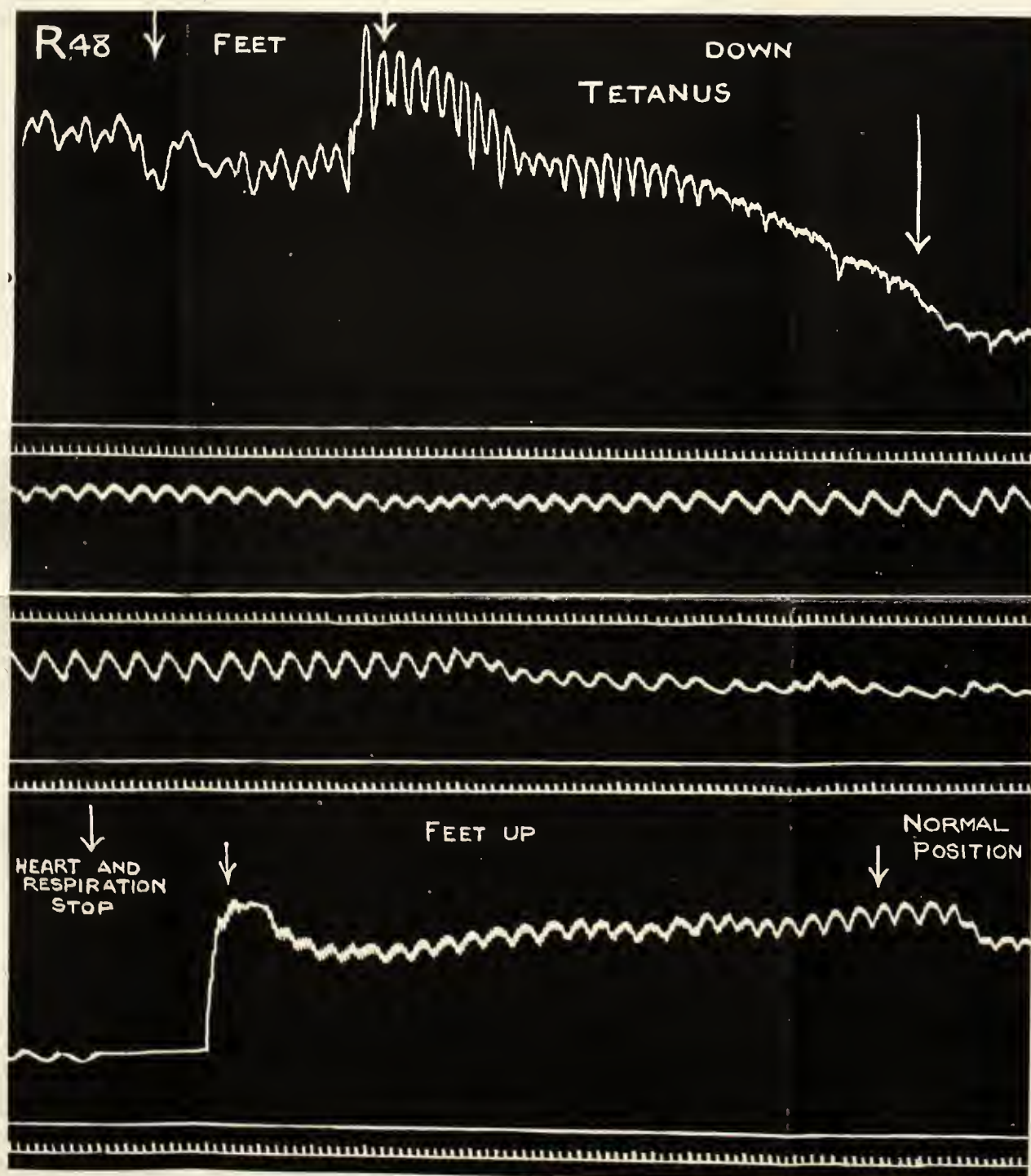


FIG. 24.—BLOOD PRESSURE OF RABBIT 48, EARLIER THAN FIG. 23, VAGI INTACT

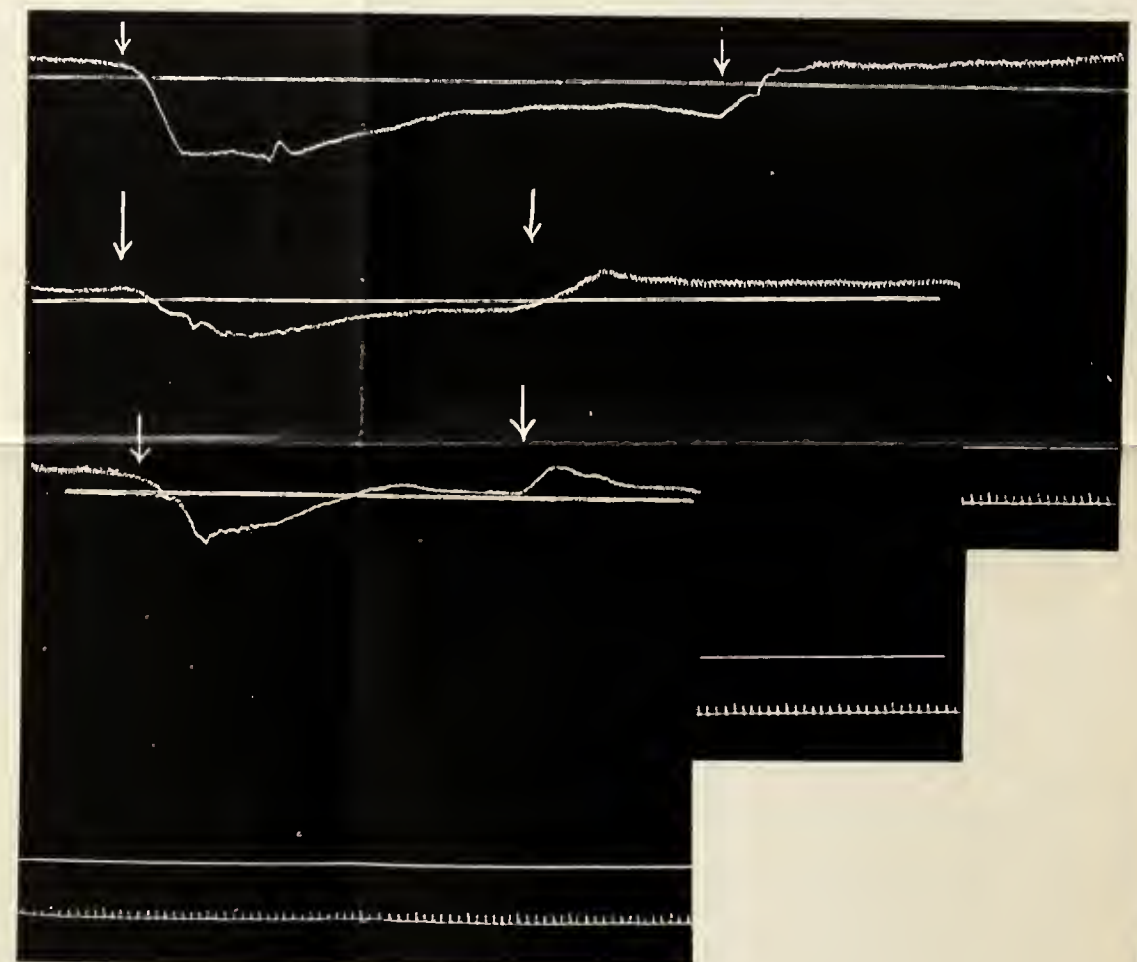


FIG. 26

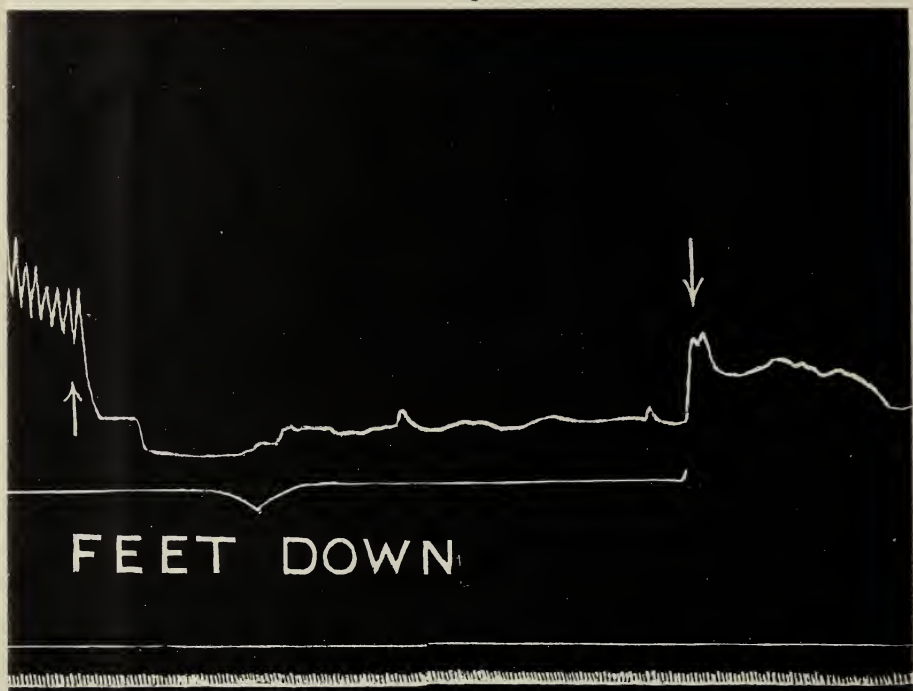
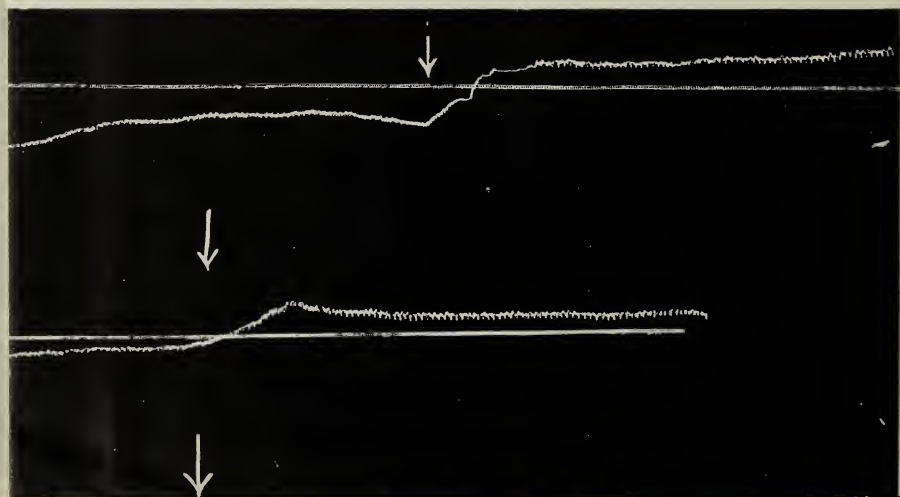


FIG. 25.



The points which have just been discussed, by natural sequence lead us to another and yet more interesting one. What will happen to the arterial pressure if the animal is made to take exercise in the erect position. Ordinarily during muscular contraction there is dilatation of the vessels in the exercised muscle. If the vaso-motor system cannot provide some compensation for this, the contracting muscles would merely form a by-pass for the blood, and would thus tend to render the brain even more anæmic than it would be owing to the erectness of the animal's position.

From this point of view Fig. 24 is of great interest. The rabbit (48, gassed) was placed in the erect position, and given intermittent stimulation by a series of short faradaic currents under the skin in the back, one electrode being near the tail, the other about the level of the kidneys, for one minute.* The blood pressure was at first raised by the muscular movements, but at the end of the stimulation it had dropped to a low level (the same is true to a less extent of the ungassed rabbit shown in Fig. 25); but after the stimulation there was no indication of the blood pressure recovering; indeed, it tended to sink gradually. On the third line of the tracing the respirations began to get irregular and on the fourth line ultimately stopped. The animal at this point was practically dead; from the experience of our other experiments there is no reason to suppose that left to himself he ever would have breathed again. When we had ascertained from inspection of the thorax that the tracing gave a just record of the respirations, or rather of the absence of respirations, we turned the animal upside down so that its head was downwards. The arterial pressure in the carotid at once leapt up, and the respiratory centre acquired its old rhythmicity; the animal had been brought back to life. From the point shown at the end of Fig. 24 the blood pressure gradually rose, and ultimately the animal regained its normal pressure (see Fig 23).†

A number of trials in the vertical (feet up) position were made. It is unnecessary to describe them in detail; the information which was derived from them was the exact complement of that yielded by the "feet down" rabbits.

Professor Sherrington pointed out to us the fact that our blood-pressure tracings of animals dying from asphyxia, not only showed no primary rise of blood pressure due to direct stimulation of the vaso-motor centre, but they showed no secondary rise due to the secretion of adrenalin.‡ We carried out a few experiments with the idea of ascertaining whether the suprarenal glands were deficient in that substance. These experiments gave a negative result; in one the glands from the gassed animal appeared to contain less adrenalin than those from an ungassed animal, in another the reverse was the case.

* The absence of cardiac slowing is due to the fact that the vagi were cut.

† The want of compensation was not shown in a rabbit (R. 38) operated in half an hour (instead of a day) after gassing (see Fig. 26).

‡ The lack of any features in the asphyxia records indicating response to suprarenal extract may be: (1) The supra renal medulla did not contain adequate adrenalin; (2) The suprarenal did not secrete the adrenalin it possessed.

Our method of testing the amount of adrenalin in the glands was as nearly as possible that used by Elliott in his experiments on adrenalin. The extracts of the glands of gassed and ungassed rabbits were made according to his method, except (1) that each extract was made up to 15 cc.; (2) we did not take quite the same precautions with regard to uniformity of speed of injection. The rabbits were killed by knocking them on the head and immediately cutting their throats. Control rabbits were the same size as the gassed rabbits.

Equal volumes of the extracts of the suprarenal from the gassed and ungassed rabbits were then injected into a normal rabbit, and the rise of arterial pressure was observed.

The extracts of the gassed and ungassed rabbits were made alternately, starting with the weakest dose, and therefore are in the order from below upwards as regards the time of their injection.

Our conclusion is that there is no qualitative difference and no very striking quantitative difference in the amounts of adrenalin in the gassed and ungassed rabbits' glands. We attribute the absence of an adrenalin rise on the tracing of arterial pressure, rather to the want of splanchnic stimulation to the glands than to the lack of adrenalin in them, as indeed V. Anrep's work would suggest. These observations are quite in accord with the theory of medullary insufficiency.

IX. THE CAUSE OF THE PHENOMENA OF SHOCK OBSERVED.

Granting that the fatal cases of delayed gas poisoning are due to incompetence of the central nervous system, and more particularly medullary centres such as the respiratory, cardio-augmentor and cardio-inhibitory and the vaso-motor centres, the question must arise what is the nature of the connection between the "gassing" and the functional nervous breakdown. Four possibilities naturally arise—

- (1) The direct effect of absorbed phosgene upon the central nervous system.
- (2) The secondary effect of insufficient pulmonary respiration.
- (3) Absorbed breakdown products from the lung tissue depressing the nervous system.
- (4) A nervous reflex from the lung having a similar effect.

In the particular cases which die as the result of exercise, there may easily be more than one of these causes at work, the central nervous system already depressed from one cause may receive "the knock-out" from another immediately associated with the exercise.

(1) *Direct Absorption of Phosgene.*

The experiments recently conducted by Leonard Hill and communicated to the War Committee of the Royal Society, indicate that in his opinion phosgene is not absorbed to any extent by moist substances, but is hydrolysed.

C. G. Douglas writes me that he also holds this opinion as the result of his own experiments.

My own work, so far as it goes, is in entire agreement with these authorities. In a single experiment conducted on a rabbit half an hour after it was gassed, the vaso-motor reflexes appeared to be normal. The blood pressure was good (Fig. 5) and when the rabbit was placed in the erect position, its power of maintaining its carotid pressure appeared to be unimpaired. This fact is shown in Fig. 26, which consists of three tracings of arterial pressure. In each tracing the animal was moved from the horizontal to the erect position with results at least as satisfactory as those shown in tracings of the blood pressure of normal rabbits under similar circumstances.

It is clear then that "delay" is an essential factor in the type of poisoning which is under discussion, and this fact is entirely against the possibility of the gas affecting the central nervous system directly.

(2) *Deficient Aeration of Blood.*

The most natural assumption is that the baneful effects of gassing are due to deficient arterialisation of the blood, either as the result of oxygen want or of excessive carbonic acid in the system or both.

We have therefore made some determinations of the gases in the blood for the purpose of getting light on this problem.

The following table gives the percentage saturation of the arterial blood in anæsthetised rabbits. The figures may be taken as within 3-4 per cent. of the correct readings.

Percentage Saturation of Arterial Blood with Oxygen.

Normal.		Gassed.	
Rabbit.	Per cent. Saturation.	Rabbit.	Per cent. Saturation.
19	94	21	93
20	94	22	93
9	93 }	49	86
	90 }	16	84
		48	70
		18	63
		30	44

The above table gives rather a misleading picture of the blood in the gassed rabbits. The fact is that 16, 49, 48 and 30 were the only gassed rabbits out of the whole series on which we experimented in which the blood appeared darker in colour than normal arterial blood, and were analysed on that account. Rabbits 21 and 22 were characteristic as far as the colour is a guide—the others are exceptional.

Indeed, one of the results for which we were least prepared was that in an animal such as rabbit 16, the blood, when the animal was first put on the dissecting table and a cannula put into its carotid, should present a normal bright appearance. Yet this animal died from 15 seconds' tetanisation. Evidently this was a typical case of

delayed phosgene poisoning. We are only on the fringe of satisfactory knowledge as regards the oxygenation of the blood in poisoning by phosgene or other pulmonary irritants, nevertheless we can say definitely that the abnormal condition of the nervous system is in many cases not due to deficiency in the percentage saturation of the arterial blood of the resting animal, at the time immediately preceding death, with oxygen.

I am aware that this statement is quite different from the general statement that the animal is not suffering from local or general oxygen want. Such might be the case even though the arterial blood was well oxygenated. Several reasons might produce oxygen want such as deficiency in the total supply of blood to the vital organs. At the moment we are only concerned with the smaller and more specific point of percentage saturation of the arterial blood, and on this we can speak confidently. Many, but not all the animals which have been gassed succeed at the time, and under the conditions of anæsthesia, of our experiments in oxygenating, up to the normal limit, all the blood which passes through their pulmonary circulation when they are at rest.

This fact seems to us to be of great importance from the point of view of general lung pathology and to merit further work, but here we need only say that it *contra-indicates the administration of oxygen at this stage.**

(3) *Toxins from the Lungs.*

Various extracts of the lung of gassed and ungassed rabbits have been injected into normal rabbits usually with considerable effect on the blood pressure, but no clear result in favour of the gassed rabbits' lungs has been obtained so far. It is proposed to continue these. The possibility is as yet by no means ruled out.

(4) *Impulses along the Vagi.*

Fig. 24 seems to indicate that delayed phosgene poisoning may cause death following on muscular exertion with both vagi cut, that have appeared in other experiments. Therefore the conduction of afferent impulses from the lung to the brain by the vagi is not an essential factor.

X. THE OXYGENATION OF THE BLOOD DURING EXERCISE.

It is well known that a normal animal oxygenates its blood as satisfactorily during exercise as when at rest, if not more so.

Two control rabbits, 19 and 20, showed that this was so in rabbits on the operating table, with respect to the muscular contraction induced by tetanisation of the back imposed in our animals.

* Note added August, 1917:—In view of the evident benefit of oxygen administration in men, more work requires to be done on this subject. It may be that the bulbar centres had been impaired by deficient oxygenation of the blood at a period earlier than that at which we operated, and that whilst the blood which passed through the functional parts of the lung was oxygenated at the time we observed it, irreparable or slowly reparable injury had been done to the central nervous system by previous and slow asphyxia.

The oxygen in these normal rabbits' blood was measured—

Period 1. Before exercise.

„ 2. During 1 minute's exercise ($\frac{3}{4}$ minute after the exercise commenced).

„ 3. Just after (about 1 minute).

„ 4. About 20 minutes after.

The following were the results—

Percentage Saturation of Arterial Blood with Oxygen.

			Period 1.	Period 2	Period 3.	Period 4.
			Per cent.	Per cent.	Per cent.	Per cent.
Rabbit 19	...	...	94	96	Spoiled.	93
Rabbit 20	...	...	94	—	95	—

These figures verify the general statement that the arterial blood remains well oxygenated in normal individuals during and immediately after exercise; but in animals which have been gassed with phosgene the day previously the result of exercise seems to be different.

The following notes were written on the inspection of the colour of the arterial blood in rabbit 16 which, after having survived $\frac{1}{4}$ -minute stimulation, died when the stimulation was repeated sometime later.

“The blood in the cannula was its normal bright colour; at 3.47 the animal was tetanised for 15 seconds, the blood grew darker in appearance, and at 3.50 it was very dark.* By 3.54 it had regained its bright appearance.”

This observation is typical. In rabbits 20 and 21, which were clearly not brought so close to death as rabbit 16, the same train of circumstances was recorded by actual measurement of the oxygen in the arterial blood.

The periods are the same as those described in discussing rabbits 19 and 20.

(1) Before exercise.

(2) During one minute's exercise.

(3) Just after exercise.

(4) About 20 minutes after exercise.

The percentage saturation of the arterial blood with oxygen were as follows :—

			Period 1.	Period 2.	Period 3.	Period 4.
			Per cent.	Per cent.	Per cent.	Per cent.
Rabbit 21	...	...	93	83	80	84
Rabbit 22	...	...	93	85	87	92

* It is possible that this resulted from diaphragmatic spasm.

These facts may be traced on the chart, Fig. 27, in which the black lines represent the changes in percentage saturation in the blood of the ungassed rabbits and the red line the gassed rabbits.

Summing up the question of oxygenation then we may say:—

The resting gassed rabbits in delayed poisoning can oxygenate their blood in most cases, but the active ones cannot.

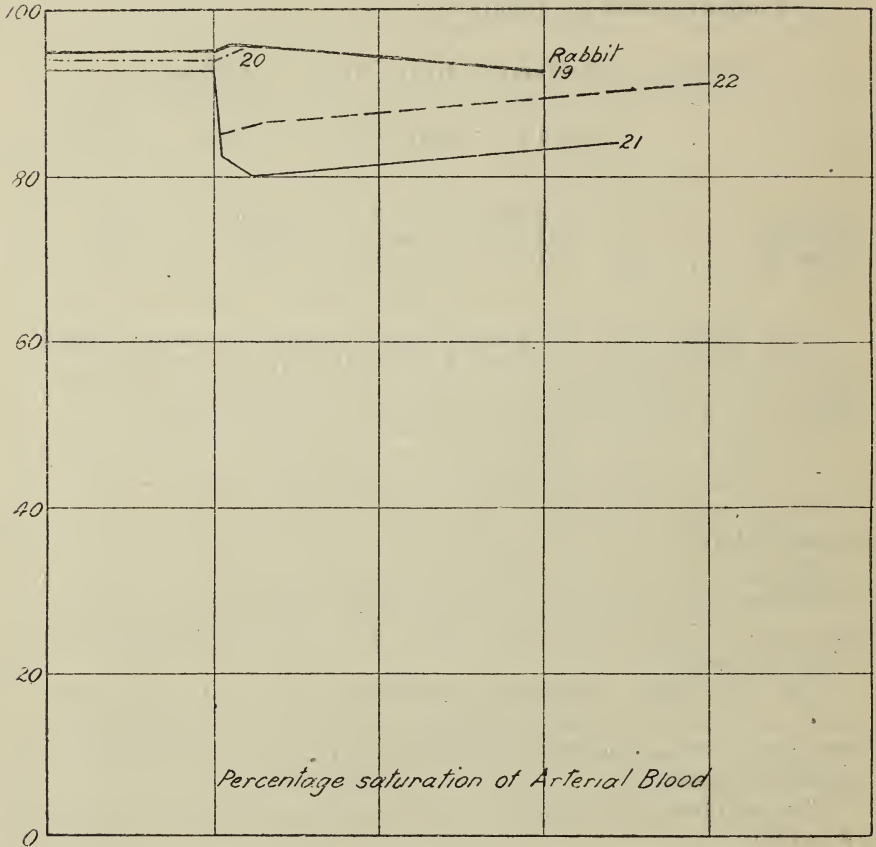


Fig. 27.

XI. ACIDOSIS.

(1) *During Rest.*

With the oxygenation of the blood goes the question of acidosis.

The method used by us of measuring the amount of acid thrust into the blood has been described on many occasions.

It consists of ascertaining the amount of oxygen which arterial blood will take up under standard conditions. The principle being that the less alkaline the blood the less oxygen will it take up. The standard oxygen pressure which we have used for rabbits' blood has been 25 mm. At this pressure normal rabbits' blood takes up oxygen to the extent of 75–85 per cent. of its total oxygen capacity.

Taking the higher limit the following are the percentage saturations of rabbits' blood with various quantities of lactic acid added (Fig. 28) :—

Added Lactic Acid.				Percentage Saturation.
0	per cent.	...	...	85
.02	"	...	...	72.5
.04	"	...	...	59
.06	"	...	...	49
.08	"	...	...	41
.1	"	...	...	35
.12	"	...	...	31
.14	"	...	...	28
.16	"	...	...	26
.18	"	...	...	25

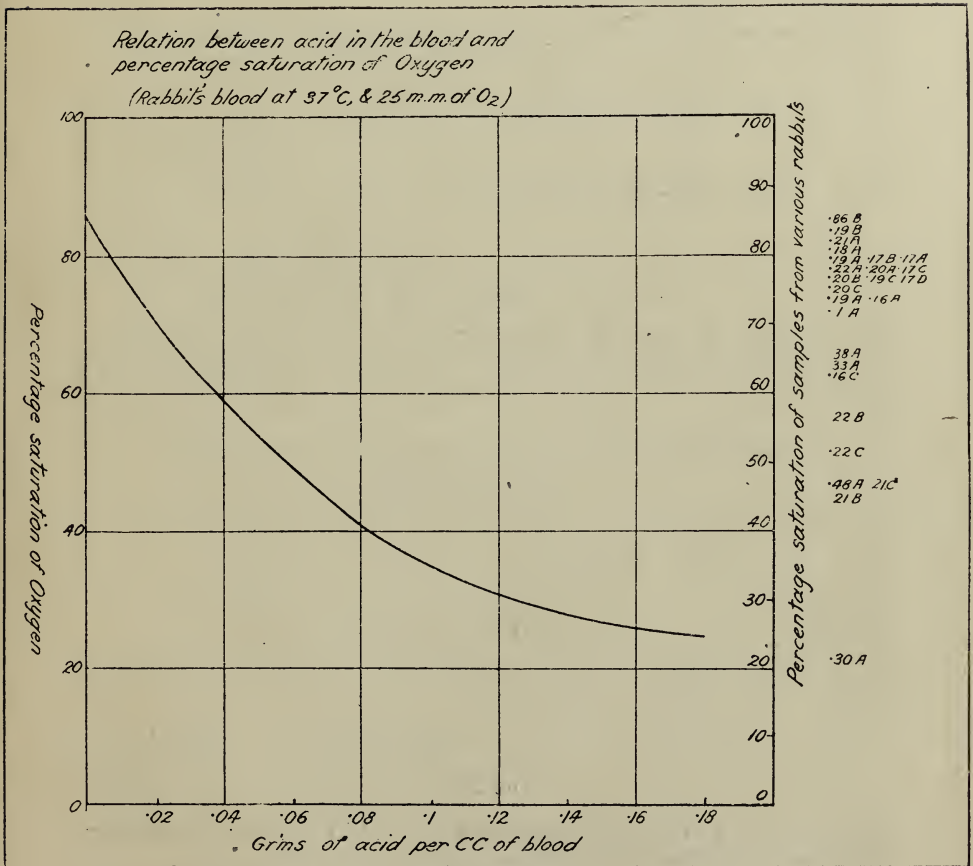


FIG. 28.

Because an animal is gassed it does not necessarily exhibit acidosis when at rest the day following the gassing, though it may do so.

For instance, rabbit 16 had some blood withdrawn from the vein in its ear before it was gassed. This blood at 25 mm. oxygen pressure was 75 per cent. saturated. It was then gassed. The next day its blood was 84 per cent. saturated under similar circumstances.

(Rabbit 16 easily succumbed to muscular exertion.)

Again, rabbits 19 and 20 yielded respectively 80 and 74 per cent. saturation the day after they were gassed.

While there is not necessarily acidosis in the resting animal, and therefore whilst it seems impossible to ascribe the condition of the C.N.S. to acidosis, there may in some cases be considerable acidosis,

*Percentage saturation of
arterial blood at 22 mm.*

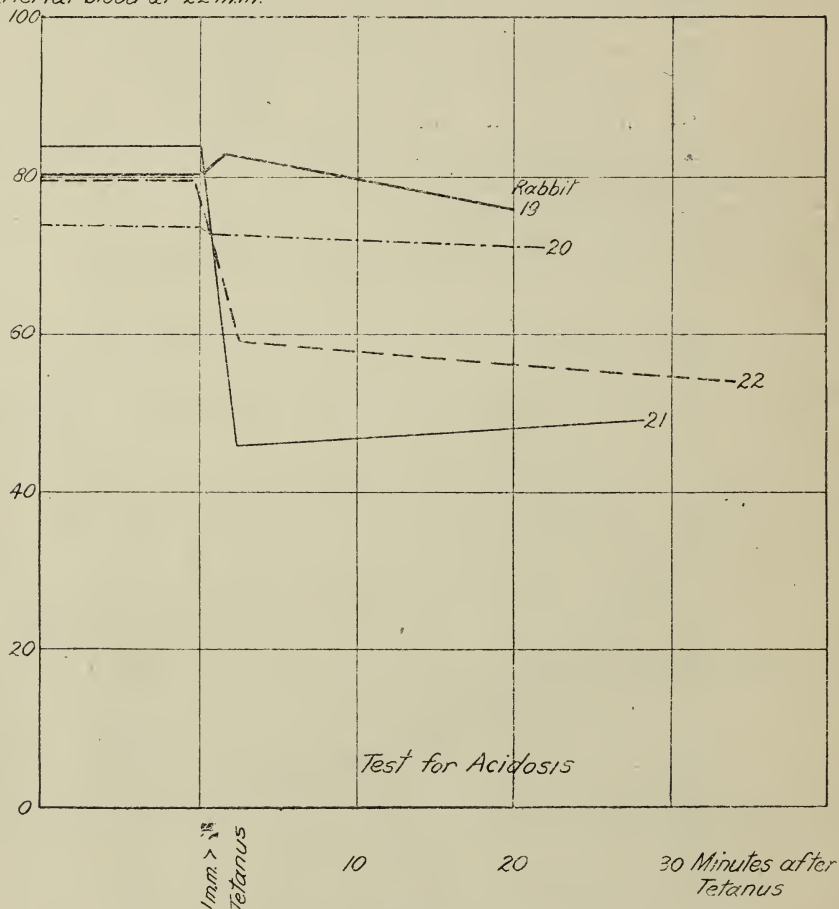


FIG. 29.

and this in a general sense seems to go hand in hand with deficiency in the aeration of the arterial blood, thus :—

				Percentage saturation of arterial blood in body.	Percentage saturation of arterial blood at 25 mm. pressure.
Rabbit	21	...	...	93	82
"	22	...	...	93	78
"	49	...	...	86	75
"	48	...	...	70	46
"	18	...	...	63	76
"	30	...	...	44	22

The exception is rabbit 18, but here the blood was taken so shortly

before death that the conditions in the animal may have been very unstable. The reaction of the blood may not have had time to respond to the deficiency of aeration. That is to say the oxygen want may have only just taken place, the reaction to it on the part of the body may not have supervened.

On the whole one cannot regard acidosis during rest as a constant phenomenon in delayed phosgene poisoning, though it may sometimes exist.

(2) *During Exercise.*

So far as the few experiments which we have been able to carry out are concerned, *a given amount of muscular contraction produces a much greater influx of acid into the blood in the gassed than in the ungassed rabbits.*

Compare, for instance, rabbits 19 and 20 (*ungassed*) with rabbits 21 and 22 (*gassed*) (Fig. 29).

The exercise given, one minute's stimulation with a faradaic current, produced scarcely any acidosis in 19 and 20, whereas it produced a very marked acidosis in 21 and 22.

The following are the percentage saturations of the blood with oxygen—

- (1) Before exercise.
- (2) One minute after exercise.
- (3) About 20 minutes after exercise.

Alongside the percentage saturations at 25 mm. O_2 pressure are given the amounts of lactic acid which would have to be added to the normal blood to make an equivalent acidosis.

Acidosis during Exercise in Gassed and Ungassed Rabbits.

(Figs. 28 and 29.)

		Ungassed.		Gassed.	
		R 19.	R 20.	R 21.	R 22.
Period 1, before muscular contraction.	Percentage saturation at 25 mm.	80	74	82	78
	Equivalent of acidosis in lactic acid.	none	·02	none	·01
Period 2, just 1 minute after muscular contraction.	Percentage saturation at 25 mm.	83	73	46	56
	Equivalent of acidosis in lactic acid.	none	·02	·07	·05
Period 3, about 20 minutes after muscular contraction.	Percentage saturation at 25 mm.	78	71	44	52
	Equivalent of acidosis in lactic acid.	none	·02	·07	·05

This degree of acidosis has been measured on several occasions in man, though not very frequently. Unfortunately there are no data as to the extent of the acidosis in man after bouts of sudden violent exercise. The observations which exist being either the result of climbing at high altitudes or of disease.

Neither of these sets of circumstances are quite comparable with the result of violent exercise in which there is probably a considerable evolution of CO_2 in the system.

The cause of this very marked acidosis in the gassed rabbits, when their muscles are thrown into contraction, is undoubtedly oxygen want in the contracting muscles.

It would not serve any useful purpose to go into the cause of the oxygen want in detail. A number of causes singly or combined may have to do with it.

- (1) The deficiency of the arterial blood in oxygen.
- (2) Insufficient blood going through the muscles, due—
 - (a) To the low arterial pressure ;
 - (b) To resistance presented by the lung to a large circulation of blood.

XII. CO_2 in the Blood.

We have done but few experiments in the CO_2 in the blood of gassed rabbits.

In two in which there was no marked acidosis the amount of CO_2 amounted to 49–53 volumes per 100 volumes of blood. This seemed to be excessive, but control results are necessary.

In one rabbit with marked acidosis the result was 36·5.

The symptoms of delayed gas poisoning do not seem at all like those of chlorine poisoning. These latter may be due to excessive CO_2 .

While the depression of the nervous system cannot be attributed to excessive CO_2 or acid, it is possible that a quick rise in the hydrogen ion concentration of the blood, taking place in exercise may give the final blow to the already unstable nervous system.

APPENDICES.

I. *Table of Doses and Duration of Doses given various Rabbits.*

Rabbit 1	...	Ungassed.	Rabbit 34	...	$\frac{1}{2}$ hour, 1/60,000.
" 2	...	1 hour, 1/60,000.	" 35	...	$\frac{1}{2}$ hour, 1/60,000.
" 3	...	$\frac{1}{2}$ hour, 1/60,000.	" 36	...	$\frac{1}{2}$ hour, 1/60,000.
" 4	...	(a) To cloths which had been exposed 1 hour. 	" 37	...	$\frac{1}{2}$ hour, 1/60,000.
" 5	...	(b) $\frac{1}{2}$ hour, 1/60,000.	" 38	...	$\frac{1}{2}$ hour, 1/60,000.
" 6	...	(c) 35 min., 1/80,000.	" 39	...	$\frac{1}{2}$ hour, 1/60,000.
" 7	...	$\frac{1}{2}$ hour, 1/60,000.	" 40	...	Ungassed.
" 8	...	$\frac{1}{2}$ hour, 1/60,000.	" 41	...	Ungassed.
" 9	...	Ungassed.	" 42	...	Ungassed.
" 10	...	Ungassed.	" 43	...	Ungassed.
" 11	...	"	" 44	...	$\frac{1}{2}$ hour, 1/60,000.
" 12	...	"	" 45	...	Ungassed.
" 13	...	$\frac{1}{2}$ hour, 1/60,000.	" 46	...	Ungassed.
" 14	...	(a) Ungassed.	" 47	...	Ungassed.
" 15	...	(b) 35 min., 1/80,000.	" 48	...	$\frac{1}{2}$ hour, 1/60,000.
" 16	...	(a) Ungassed.	" 49	...	$\frac{1}{2}$ hour, 1/60,000.
" 17	...	(b) 35 min., 1/80,000.	" 50	...	$\frac{1}{2}$ hour, 1/60,000.
" 18	...	$\frac{1}{2}$ hour, 1/60,000.	" 51	...	Ungassed.
" 19	...	$\frac{1}{2}$ hour, 1/60,000.	" 52	...	Ungassed.
" 20	...	$\frac{1}{2}$ hour, 1/60,000.	" 53	...	$\frac{1}{2}$ hour, 1/60,000.
" 21	...	$\frac{1}{2}$ hour, 1/60,000.	" 54	...	$\frac{1}{2}$ hour, 1/60,000.
" 22	...	$\frac{1}{2}$ hour, 1/60,000.	" 55	...	Ungassed.
" 23	...	$\frac{1}{2}$ hour, 1/40,000.	" 56	...	Ungassed.
" 24	...	$\frac{1}{2}$ hour, 1/40,000.	" 57	...	Ungassed.
" 25	...	Ungassed.	" 58	...	Ungassed.
" 26	...	Ungassed.	" 59	...	(a) Gassed (?).
" 27	...	$\frac{1}{2}$ hour, 1/60,000.	" 60	...	(b) $\frac{1}{2}$ hour, 1/60,000,
" 28	...	$\frac{1}{2}$ hour, 1/60,000.	" 61	...	fortnight later.
" 29	...	$\frac{1}{2}$ hour, 1/60,000.	" 62	...	(c) $\frac{1}{2}$ hour, 1/60,000,
" 30	...	20 min., 1/60,000.	" 63	...	next day.
" 31	...	20 min., 1/60,000.	" 64	...	(a) 21st Mar. $\frac{1}{2}$ hour,
" 32	...	Ungassed.	" 65	...	1/60,000.
" 33	...	Ungassed.	" 66	...	(b) 22nd Mar. $\frac{1}{2}$ hour,
			" 67	...	1/60,000.
			" 68	...	(c) 23rd Mar. $\frac{1}{2}$ hour,
			" 69	...	1/26,000.
			" 70	...	Ungassed.
			" 71	...	Ungassed.
			" 72	...	Ungassed.

II. *Percentage Saturation of Oxygen in Various Samples of Rabbits'*
Blood exposed to 25 mm. of O₂.

Sample.	Conditions when Sample was taken.	Percentage of O ₂ .	—
1A	From ear before operation	71	} Ungassed.
1B	From carotid after operation	81 (?)	
16A	From ear before gassing	{ 76.5	
16B	From ear after $\frac{1}{2}$ hour gassing	74.5	} Gassed.
16C	From carotid 20 minutes after $\frac{1}{4}$ minute tetanisation.	84.5	
		62	
17A	From ear	80.5	} Ungassed.
17B	From carotid after luminal and ether ...	80.5	
17C	1 minute after $\frac{1}{4}$ minute tetanisation ...	{ 79.5	
17D	1 minute after 1 minute tetanisation ...	77	} Ungassed.
18A	From carotid during operation just before death; no tetanisation and no struggling.	81.5	
19A	From carotid before tetanisation ...	80	} Ungassed.
19B	1 minute after 1 minute continuous tetanisation.	83	
19C	20 minutes later	{ 76	
20A	Before tetanisation	78	
20B	1 $\frac{1}{2}$ minutes after 1 minute continuous tetanisation.	74	
		73	
20C	23 minutes later	71	} Gassed.
21A	Before tetanisation	83	
21B	1 $\frac{1}{2}$ minutes after 1 minute intermittent tetanisation.	44.5	
21C	25 minutes later	46.5	
22A	Before tetanisation	78	
22B	2 minutes after 1 minute intermittent tetanisation.	56.5	
22C	25 minutes later	51.5	} Gassed.
30A	At beginning of operation; exact point difficult to determine below 23 per cent. Heart dilated.	21	
33A	After 1 minute intermittent tetanisation	64.5	} Gassed.
38A	From carotid at beginning of operation	65.5	
48A	At beginning of operation from carotid	{ 44.5	
		48.5	

III. *Temperature of Gassed Rabbits approximately 18 Hours after Exposure to Gas. Average Temperature of Ungassed Rabbits being 101.4° F.*

Rabbit.	Time and date.	Temperature (F).	Condition.
4	5.40 p.m., February 17th, 1916 ...	101.4°	Ungassed.
4	10.30 a.m., February 18th, 1916 ...	102°	Gassed $\frac{1}{2}$ hour overnight.
4	11 a.m., February 25th, 1916 ...	101.4°	Gassed $\frac{1}{2}$ hour overnight.
11	Next morning after being gassed in evening.	102.4°	Gassed.
12	Next morning after being gassed in evening.	101.6°	Gassed.
16	Next morning after being gassed in evening.	101.4°	Gassed.

IV. *Circumstances Attending Deaths of Various Rabbits.*

[N.B.—All exposed $\frac{1}{2}$ hour to 1/60,000 unless otherwise stated.]

Found dead next morning.	Died after struggling and excitement.	Died after tentanisation.	Died during Operation.	Killed at end of operation.	Did not die.
No. 2 (1 hr.) No. 13 No. 15 Nos. 23, 24 (1/40,000, $\frac{1}{2}$ hr.) Nos. 34, 35 (45 min.) No. 44	No. 3 No. 14 Nos. 5, 18 very slight or no.	No. 10 No. 16 No. 29 No. 48 (revived)	No. 22 No. 28 No. 31 asphyxn. (20 min.). No. 32 (accidental). Nos. 38, 49 (accidental). No. 50	No. 21 No. 30 (20 min.). Nos. 36, 37 (killed for Mrs. Tribe's operation). No. 48	No. 4 exposed to cloths for night. No. 4, $\frac{1}{2}$ hr. No. 4, 35 min., 1/80,000. N.B.—Died of pneumonia. No. 11 (35 min., 1/80,000). No. 12 (35 min., 1/80,000). No. 39 (killed for lung extract). No. 53, 54 (killed for supra- renals). No. 59 (after 3(?) gassings, killed for suprarenal extract). No. 60 (gassed twice).



V. *Sample Protocols of Experiments.*

Rabbit 1. Date, February 9th, 1916. *Not exposed to Gas.*

12.20 p.m.—Blood taken from ear for analysis. (A).

12.30 p.m.—Injected with 8 cc. of 5 per cent. solution luminal sodium.

2.33—2.45 p.m.—A.C.E. given.

Blood pressure taken from carotid. (See Chart.)

3.20 p.m.—Intestine removed.

3.56 p.m.—Venous blood from kidney, &c., taken.

3.59 p.m.—Arterial blood from kidney, &c., taken.

Results :—

O₂ used per minute 376 cub. mm.

Blood flow per minute 17.14 cc.

Weight of kidney 8.26 grms.

4 p.m.—Blood taken for analysis. (B).

Percentage saturation of O₂ at 27 mm. pressure of O₂.

12.20 p.m. specimen .. 75 per cent. A.

4 p.m. specimen .. 84 per cent. B. (This analysis did not go very smoothly.)

Rabbit 2. Date, February 11th and 12th, 1916.

Gassed Exposure, 1 hour.

5-6 p.m., February 11th, 1916.—Exposed for 1 hour to 1/60,000 phosgene.

8 a.m., February 12th, 1916.—Found dead and cold.

P.M. at University College Hospital, London.

Lung

Stomach (superficial erosions)

Kidney

Liver

} In 5 per cent. formalin and normal salt at U.C.H.

No hæmoglobin in the bladder.

Histological report :—

Lungs: One piece collapsed. Alveoli all fully œdematous throughout.

Heart: No fatty degeneration.